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Cost-effectiveness of telehealthcare to patients with chronic obstructive pulmonary disease: Results from the Danish "TeleCare North" cluster-randomized trial.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-014616
Article Type:	Research
Date Submitted by the Author:	07-Oct-2016
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Primary Subject Heading:	Health economics
Secondary Subject Heading:	Health policy, Medical management, Patient-centred medicine
Keywords:	BIOTECHNOLOGY & BIOINFORMATICS, Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS, HEALTH ECONOMICS

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Cost-effectiveness of telehealthcare to patients with chronic obstructive pulmonary disease: Results from the Danish “TeleCare North” cluster-randomized trial

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ABSTRACT

Objectives: To investigate the cost-effectiveness of a telehealthcare solution in addition to usual care compared with usual care.

Design: A 12 months cost-utility analysis conducted alongside a cluster-randomized trial.

Setting: Community based setting in the geographical area of North Denmark Region in Denmark.

Participants: 26 municipality districts define randomization clusters with 13 districts in each arm. 1,225 patients with chronic obstructive pulmonary disease were enrolled of which 578 patients were randomized to telehealthcare and 647 to usual care.

Interventions: In addition to usual care, patients in the intervention group received a set of telehealthcare equipment and were monitored by a municipality-based healthcare team. Patients in the control group received usual care.

Main outcome measure: Incremental costs per quality-adjusted life-years gained from baseline up to 12 months follow-up.

Results: From a healthcare and social sector perspective, the adjusted mean difference in total costs between telehealthcare and usual care was €728 (95% CI: -754; 2211) and the adjusted mean difference in quality-adjusted life-years gained was 0.0132 (95% CI: -0.0083; 0.0346). The incremental cost-effectiveness ratio was €55,327 per quality-adjusted life-year gained. Decision-makers should be willing to pay more than €55,000 to achieve a probability of cost-effectiveness greater than 50%. This conclusion is robust to changes in the definition of hospital contacts and reduced intervention costs. Only in the most optimistic scenario combining the effects of all sensitivity analyses, does the incremental cost-effectiveness ratio fall below UK thresholds values (€21,068 per quality-adjusted life-year).

Conclusions: Telehealthcare is unlikely to be a cost-effective addition to usual care if it is offered to all patients with chronic obstructive pulmonary disease and if the willingness-to-pay threshold values from National Institute for Health and Care Excellence are applied. Since no willingness-to-pay threshold exists in Denmark, it may still be cost-effective here.

Trial registration: Clinicaltrials.gov, NCT01984840, November 14, 2013.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study reports the within-trial cost-effectiveness of a pragmatic large-scale asynchronous telehealthcare initiative requested by systematic reviews in order to improve the international evidence base of the economic effects of telehealthcare for COPD patients.
- A relatively broad health care and social sector perspective was chosen and the cost-analyses of resource use are based on register data.
- The way telehealthcare was implemented may have affected cost-effectiveness. The involved organizations and healthcare professionals underwent a steep learning curve after implementation of the telehealthcare solution, where they had to find new ways of working together and adapt to new work procedures.
- The included participants presumably had stable COPD and it is unknown if inclusion of patients with more acute COPD would have improved cost-effectiveness.

Keywords: RCT; Telehealth; Telecare; Telemonitoring; COPD; Economic Evaluation; Cost-effectiveness; Denmark

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the most prevalent and deadly diseases in the world (1). The global prevalence of COPD is high (11,7%) (2). COPD is associated with high mortality (3), presence of comorbidities (4,5) and reduced health-related quality-of-life (6,7). COPD poses a substantial financial burden on healthcare systems, e.g. the annual direct costs for COPD has been estimated to \$20-26 billion in the US with hospital admissions representing 52-70% of all direct costs (8). A recent Danish study has estimated that COPD is responsible for 8,300 years of life lost and €174 million in annual direct cost for treatment and care (9).

Telehealthcare has been suggested as a possible effective intervention to patients suffering from COPD on especially health-related quality-of-life (10). Telehealthcare is a technology that contains data from a patient which is transferred electronically over a physical distance and healthcare professionals exercise their judgment in providing personalized feedback to the patient based on these data (11). Some feasibility studies including cost-analyses have previously suggested an added value of telehealthcare compared to usual practice and some of these studies show that telehealthcare may lower hospital or healthcare costs (12–16). But most recent systematic reviews have questioned the quality of this evidence and have requested more cost-effectiveness evaluations (17–21), preferably with broader cost-perspectives (22).

The objective of this paper is to add to this international evidence base on the cost-effectiveness of telehealthcare by presenting the results of a cost-utility analysis of a telehealthcare intervention to patients with COPD compared with usual practice. The analysis was nested within a 12-months cluster-randomized trial (called “TeleCare North”) that were conducted in the geographic area of North Denmark Region in Denmark from 2013-2014.

METHODS

A more detailed trial protocol has been published elsewhere (23), but a brief summary is provided in Table 1. 26 municipality districts in North Denmark Region define the randomization clusters with 13 districts in each arm. In addition to usual care, patients in the intervention group received a set of telehealthcare equipment and were monitored by a community-based healthcare team. Patients in the control received usual care.

Table 1: Description of the Danish TeleCare North cluster-randomized trial	
Eligible criteria for clusters	All municipalities in North Denmark Region except one (a small island off the coast), 10 municipalities in all. Each municipality consisted of between 2 and 5 municipality districts and these districts were randomization units, 26 municipality districts in total (13 in each arm).

Eligible criteria for patients	COPD as primary disease, diagnosis by spirometry, in treatment according to GOLD guidelines, at least two exacerbations within the past 12 months, motivated for treatment, fixed residence in North Denmark Region, The Modified Medical Research Council scale (mMRC) ≥ 2 or mMRC ≥ 3 and COPD Assessment Test (CAT) ≥ 10 . Exclusion criteria were: no phone line or GSM coverage, unable to understand Danish sufficiently to complete the study questionnaires or diagnosed with a cognitive impairment.
Intervention group: Cluster-level intervention	Municipality district healthcare personnel (primarily nurses and health assistants) were trained in two separate sessions. One session focused on the technical aspects of the tablet and physical measurements. Another session focuses on general disease awareness and communication with patients. The training was performed by members of the trial administration office. General practitioners were responsible for establishing threshold values for physical measurements. Nurses in the patient's residing municipality were responsible for monitoring the data obtained and should incorporate monitoring time duties with their existing job responsibilities. Exemptions were COPD patients receiving oxygen therapy and COPD patients with open hospital admissions who were monitored at their hospital as usual. Patients were monitored asynchronously by a nurse on a daily basis. Measurements were classified with either a green, yellow or red code (Green code: no threshold values were exceeded. Yellow code: one or more values exceeded the threshold values. Red code: one or more values exceeded the threshold values and had not previously been recorded). The nurse had the option to contact the patient by telephone and/or the patient's general practitioner and/or dispatch an ambulance. Installation, swopping of defects, deinstallation and technical support and maintenance of the equipment was handled by IT-specialists.
Intervention group: Patient-level intervention	Telephone contact to each patient from municipality healthcare personnel no later than 10 days after randomization, and a 45-minute appointment scheduled for patients who wanted to receive the tablet at home. For those who wished to receive the tablet at a municipality health center, a 75-minute appointment was scheduled with 3 to 4 patients in each group. At both appointments, a nurse from the patients' municipalities demonstrated the use of the tablet and instructed patients in how to conduct physical measurement. Patients were asked to measure their vital signs daily during the first two weeks (both weekdays and weekends) and 1 to 2 times weekly after the two first weeks. A 45-minute follow-up visit was scheduled 3 to 4 weeks after the first appointment to check if the patient used the device appropriately and if the threshold values of the physical measurements needed to be adjusted.
Intervention group: Device	All patients received the same device and peripherals. It consisted of a standard tablet (Samsung Galaxy) containing information on handling COPD in general and software (two apps) that automatically instructs the patient in handling COPD during exacerbations. The tablet can collect and wirelessly transmit data on blood pressure, pulse, blood oxygen saturation, and weight via an attached Fingertip Pulse Oximeter, a Digital Blood Pressure Monitor, and a scale.
Control group: Usual Care	Usual practice for caring for patients with COPD is the responsibility of the patient's general practitioner (treatment and monitoring) and the municipalities (practical help and home nursing care). COPD patients can make appointments with their general practitioner or call the emergency contact number without copayment in order to get treatment or advice in managing COPD but this advice is not personalized. Community care administered by municipality district personnel comes at regular intervals based on a clinically based estimate of the patients' needs, but these personnel are not necessarily certified nurses and often not fully educated in COPD and not on call.

GOLD: Global initiative for chronic obstructive lung disease

COPD: Chronic obstructive pulmonary disease

GSM: Global system for mobile communications

The primary outcome measure for the cost-effectiveness analysis was the incremental cost-effectiveness ratio (ICER) expressed as the total cost per quality-adjusted life-years (QALY) gained measured from baseline to follow-up at 12 months. In defining the total costs, this trial adopted a healthcare and social care sector perspective (including hospital services, primary care, medicine, home care services and rehabilitation).

Healthcare service use and healthcare costs

Healthcare and social care service use were all estimated based on register data by applying a unique civil registration number that all Danish citizens have and that makes precise linkage between registers possible. National patient-level data for all hospital contacts were collected from the Danish National Patient Register (24), which contains all inpatient, outpatient and emergency ward visits in Denmark. The total costs for each contact is a variable in these datasets and are valued based on the diagnose-related group (DRG), the actual procedures conducted and the duration of the contact (25). The included admissions, outpatient and emergency ward visits were in the main analysis restricted to those defined as COPD-specific in the Danish Register for COPD (26).

All contacts between patients and the primary care sector were collected from the National Health Insurance Service Register (27). The costs for each contact is part of the dataset and are valued based on fees negotiated in a collective agreement (28). At present, it is not possible to identify the cause of contact to the primary care sector, so all contacts are included.

Medication use was taken from The Danish Register of Medicinal Product Statistics that contains information about the total sales of medicinal products in Denmark (29) and are restricted to medicine associated with COPD (R03 ATC codes), specific antibiotics, antifungals and medicine for anxiety, all associated with the treatment of COPD-exacerbations as well as medicine for smoking cessation. The costs for each product is given in this dataset and is valued based on a standardized pharmacy consumer price (30).

Patient-level community care service use was collected from individual care systems in each of the 26 included municipality districts. The type and duration of standard care activities such as personal care, practical help, home nursing care and rehabilitation activities are routinely recorded for each contact. Each municipality district values contacts differently based on an internal calculated mean hourly cost. It was pragmatically decided to value time consumption in municipality districts as an average of the reported hourly costs from municipality districts. Four of the 26 municipality districts in the trial were implementing a different IT-system at the time of data collection which meant that rehabilitation costs for these four municipality districts were unavailable (2 municipality districts in the telehealthcare group and 2 in the usual care group).

Healthcare service use was collected 12 month prior to randomization and up to 12-months follow-up to allow for both within-trial and potential baseline differences in costs to be calculated.

Intervention costs

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Costs associated only with the clinical trial, preparing the organization and developing the telehealthcare solution were excluded. Intervention costs were costs of hardware and peripherals, installation and deinstallation costs, maintenance and support costs, training costs for healthcare professionals, patient specific training, monitoring costs and project management costs.

Per person costs of the “package” of telehealthcare equipment (the so-called “Telekits” consisting of a tablet and peripherals) were calculated. The “Telekits” supplied were exactly the same for all patients and was purchased to each patient ahead of the trial and valued as prices paid. The per person costs of installation/deinstallation and swopping any defects in the equipment was negotiated with an external supplier prior to the trial and valued as prices paid. Per patient maintenance and support costs consisted of software licenses and data charges, technical support to patients and healthcare professionals as well as IT-infrastructure- and application maintenance and valued as prices paid. Costs associated with IT-infrastructure- and application maintenance was not dependent on the number of patients in the trial but the software and hardware configuration employed by the telehealthcare solution which could in principle include all COPD patients and patients with chronic heart failure. It was decided to allocate these costs on the estimated number of COPD and chronic heart failure patients in North Denmark Region (10,500 patients) (31,32). The per patient costs of training healthcare professionals were based on planned time spent conducting education workshops in COPD disease awareness and the telehealthcare solution, the number of conducted workshops and the average hourly wage for a community district nurse. Per patient costs of patient specific training were based on planned time and valued based on a mean hourly wage for a community district nurse. Time spent per patient on monitoring were estimated by time registries in the municipality districts and valued based on a mean hourly wage for a community district nurse. Based on the experiences gained with the implementation in the trial period, it was estimated that it would be necessary to have an administrative officer employed to “run” the telehealthcare solution, should it be implemented in routine practice (coordinating activities, contract supervision etc.). Project management costs were valued as mean yearly salary for an administrative officer including all standardly available pensions and pay supplements (33). As with IT-infrastructure- and application maintenance, these costs could be allocated on more patients than in the trial and they were therefore also allocated on the estimated number of COPD and chronic heart failure patients in North Denmark Region (10,500 patients) (31,32).

Equipment costs (the Telekits), installation/deinstallation costs, costs associated with training healthcare professionals and patient specific training were annuitized over a period of five years with a discount rate of 3% p.a. and presented as

equivalent annual cost. 5 years can be used as standard lifetime for “other IT-equipment” in Danish capital accounting (34) and has been used in previous telehealthcare research (12,35).

All costs are reported in 2014 prices. Costs were obtained in Danish kroner (DKK) and exchanged to Euro (€) using the average 2014 exchange rate (1€ = 7.4547DKK). All healthcare service use and costs are reported as means and standard errors and where descriptive statistics are presented, differences between intervention and control group means are reported as raw differences and, to allow for future meta-analysis, as standardized differences (the raw difference between group means, divided by the standard deviation of the total sample) presented as a percentage.

Effectiveness

Information of mortalities were obtained from the Danish Register of Causes of Death (36) which contain mortality statistics on all deaths in Denmark. Utility scores stem from the EQ5D-3L health-related quality-of-life questionnaire with Danish societal weights (37). QALYs were calculated by linear interpolation of utility scores. The health-related quality-of-life items and relevant demographic data were collected at baseline by help from the patients’ general practitioners who distributed the questionnaires to all patients but with a prepaid return envelope to the trial administration office. At follow-up, a questionnaire consisting of the health-related quality-of-life items were sent from the trial administration office to the patients’ home addresses with a prepaid return envelope.

ANALYSIS

Statistical analyses were all performed in STATA version 12.1 except the probabilistic sensitivity analysis that was developed in Microsoft Excel 2010.

Missing data

1,225 patients were randomized in the study (578 patients in the telehealthcare group and 647 in the control group). At baseline, complete data for the EQ5D score were available for 530 patients in the telehealthcare group and 594 patients in the usual care group. Complete data for both total costs (i.e. all cost-categories), baseline EQ5D-score and EQ5D-score at follow-up were available for 751 patients (61%; 325 in telehealthcare group; 426 in control group). 302 patients (25%; 169 in telehealthcare group; 133 in control group) were lost to follow-up at 12 months. 172 patients (14%; 84 in telehealthcare group; 88 in control group) had incomplete registrations of EQ5D scores at either baseline or follow-up or missing rehabilitation costs.

Current good practice for trial-based economic evaluation recommends that analyses should account for missing/censored data by imputation, especially when there is a large amount of missing data (38). Therefore, missing

data on EQ5D scores, rehabilitation costs and baseline characteristics for patients lost to follow-up and incomplete cases were imputed using the *mi impute chained* command in STATA12.1 and 30 complete datasets were created. Imputation models followed the principles recommended by Faria and colleagues (39) and included outcome variables, predictors for the outcomes at both time points, predictors for missing observations in the individual variables. The imputation models were estimated separately by treatment group and included the clustering variable, measures of health-related quality-of-life (EQ5D scores), costs at baseline or at 12 months follow-up (in the categories presented in Table 4), measures of disease status (forced expiratory volume in one second (FEV1%), forced vital capacity (FVC%), diastolic- and systolic blood pressure), smoking status, presence of comorbidities (diabetes, cancer, cardiovascular disease, mental illness or musculoskeletal disorders) and socio-demographic variables (age, gender, marital status, education and employment status).

Cost-effectiveness analysis

The cost-effectiveness analysis followed an intention-to-treat principle. The statistical analysis applied multilevel modeling for continuous variables (40), which has been suggested as an analysis strategy for cost-effectiveness research of cluster-randomized trials (41).

To allow for different sets of covariates, estimation of incremental total costs and incremental QALYs gained was based on two separate linear mixed effects models; one for total costs and one for QALYs. Total costs were controlled for treatment arm, baseline EQ5D score, baseline costs (total costs 12 months prior to randomization), age, baseline FEV1%, presence of musculoskeletal disease (a significant cost driver in municipality districts) and clustering. QALYs gained were controlled for treatment group, baseline EQ5D score, age, gender, baseline FEV1%, marital status, presence of diabetes, presence of cancer and clustering. These estimations were facilitated by the *mi estimate: xtmixed* command with robust standard errors. A deterministic ICER-estimate was calculated using the treatment beta-coefficients from these two models. In order to explore the uncertainty surrounding cost-effectiveness, the output from the *mi estimate: xtmixed* was exported to Microsoft Excel 2010 along with Cholesky's decomposition matrix to allow for a potential correlation between all the parameters in the analyses models. By redrawing new parameter estimates from the estimated treatment-effect with its standard error, 5,000 simulations were calculated to obtain new estimates of incremental QALYs and incremental total costs which were used to construct cost-effectiveness acceptability curves.

Sensitivity analysis 1: All-cause hospital contacts

In the base-case analysis, we have sought to limit hospital contacts to COPD-specific contacts because the hypothesis were that telehealthcare could prevent a proportion of admissions and emergency ward visits associated with exacerbations and make most COPD-specific outpatient control visits redundant. However, the included patients suffer from a variety of diseases concomitant with COPD (see Table 2). As part of the intervention, it is therefore plausible that a more integrated care and monitoring approach assisted by the telehealthcare technology could also prevent some hospital contacts due to comorbidities. Some of the measurements facilitated by the Telekits could e.g. be indicative of cardiovascular disease and especially chronic heart failure. The effect on incremental costs of including all hospital contacts was therefore explored.

Sensitivity analysis 2: Reduced procurement prices and larger scale

Potential discounts on procurement prices and increased capacity of the telehealthcare solution could drastically reduce intervention cost thereby affecting the cost-effectiveness conclusion. Therefore, an effect of a 30% discount on Telekit equipment, installation, support and maintenance was explored. 30% is an estimate stemming from experiences with negotiating procurement prices subject to large-scale implementation of telehealthcare in the Danish healthcare sector (42). In addition, suppliers have stated that the costs of maintenance (IT-infrastructure and applications) and support costs does not depend on the number of patients included, but the complexity of the hardware and software configuration. The effects of making these costs negligible due to very large-scale implementation were therefore also explored.

Sensitivity analysis 3: Reduced monitoring time

Municipality healthcare personnel had a steep learning curve for their new monitoring tasks and the patients' need for monitoring was uncertain at the outset. This resulted in approximately 5 minutes of average monitoring time per patient per week in the trial. After 12 months, personnel have become more efficient at monitoring and responding to vital values, so a new average target of 2 minutes per week per patient (i.e. 110 minutes annually) have been discussed by the North Denmark Region and the municipality districts (43) and the effects of this target on cost-effectiveness is investigated.

Finally, a most optimistic scenario exploring the combined effect of sensitivity analyses 1, 2 and 3 was investigated. The effect on total costs and/or QALYs was explored using the same models and covariates as the base-case analysis.

RESULTS

Baseline characteristics of all the included patients are presented in Table 2. Baseline characteristics are fairly balanced across treatment groups with no more statistically significant differences than could be expected by chance. The FVC(%) is significantly lower in the telehealthcare group and there is an overall tendency for patients in the telehealthcare group to have slightly worse health (lower average lung function, lower average health-related quality of life, higher average proportion of comorbidities (except musculoskeletal disorders)). Baseline costs were also higher in the telehealthcare group.

Table 2: Baseline characteristics			
	All 1,225 participants at baseline		
	Telehealthcare	Usual care	Difference
	<i>n</i> =578	<i>n</i> =647	<i>Raw</i>
Age (years)§	69.55 (9.36)	70.33 (9.11)	-0.78
Men (%)§	48.27 (n=279)	43.74 (n=283)	4.53
Marital status (%)			
Married/In a relationship	55.88 (n=323)	54.25 (n=351)	1.63
Single	20.42 (n=118)	22.10 (n=143)	-1.68
Widow/Widower	16.78 (n=97)	16.54 (n=107)	0.24
Missing (%)	6.92 (n=40)	7.11 (n=46)	-0.19
Smoking status (%)			
Non-smokers	59.34 (n=343)	63.06 (n=408)	-3.72
Smokers	33.91 (n=196)	29.21 (n=189)	4.70
Missing (%)	6.75 (n=39)	7.73 (n=50)	-0.98
Duration of COPD (years)	7.80 (6.23)	7.70 (5.79)	0.10
Missing (%)	14.01 (n=81)	15.14 (n=98)	-1.13
FEV1(%)	47.70 (18.05)	48.37 (18.94)	-0.67
Missing (%)	18.51 (n=107)	19.78 (n=128)	-1.27
FVC(%)	70.38 (20.02)	74.34 (22.33)	-3.96**
Missing (%)	34.43 (n=199)	39.41 (n=255)	-4.98
Comorbidities (%)			
Diabetes	10.21 (n=59)	9.89 (n=64)	0.32
Coronary heart disease	32.70 (n=189)	31.84 (n=206)	0.86
Mental health problem	4.84 (n=28)	4.79 (n=31)	0.05
Musculoskeletal disorder	24.91 (n=144)	29.37 (n=190)	-4.46
Cancer	6.06 (n=35)	4.79 (n=31)	1.27
Missing (%)	8.13 (n=47)	7.88 (n=51)	0.25
Baseline total costs (€)§	6492 (14150)	4900 (7149)	1592
Missing (%)	13.66 (n=79)	11.28 (n=73)	2.38
Baseline EQ5D	0.706 (0.202)	0.716 (0.185)	-0.010
Missing (%)	8.30 (n=48)	8.19 (n=53)	0.11

Data are mean (standard deviation) or proportion (number of patients)
COPD: chronic obstructive pulmonary disease; FEV1(%): forced expiratory volume in one second of predicted normal;

FVC(%): forced vital capacity

§Variable has no missing values

\$Baseline total costs are missing for 3 cost categories (Help and care at home, Community or district nurse and Rehabilitation, see Table 4) in 4 municipality districts

*Fischer's exact test for difference in proportions of patients in telehealthcare group and usual care group (at baseline, for complete cases, for lost to follow-up and for incomplete cases), $P < 0.05$

**Mann-Whitney's test for differences in mean in telehealthcare group and usual care group (at baseline, for complete cases, for lost to follow-up and for incomplete cases), $P < 0.05$

The unadjusted healthcare service use over the trial period with unit costs sources is summarized in Table 3. Average values for healthcare service use were not imputed (i.e. values are based on non-missing cases unadjusted for patient case mix). Table 3 reveals that resource use is consistently higher in the telehealthcare group.

Table 3: Service use at 12 months across treatment groups and applied unit costs

	Mean (SE) contacts		Between group difference		Unit	Unit cost
Service use	Telehealthcare (n=578)	Usual care (n=647)	Raw	Standardized (%)*		
<i>Hospital contacts</i>						
Admissions	0.5 (0.05)	0.45 (0.49)	0.046	3.70	Per contact	DRG value of contact (25)
Inpatient bed days	2.69 (0.31)	2.60 (0.31)	0.09	1.18	Per contact	Included in DRG value of contact (25)
Outpatient/emergency department visits	0.87 (0.08)	0.74 (0.07)	0.13	7.16	Per contact	DRG value of contact (25)
<i>Primary care contacts</i>						
General practitioner	10.72 (0.35)	9.92 (0.33)	0.80	9.35	Per contact	Tariffs from Collective agreement (28)
<i>Municipality care (time spent)</i>						
Help and care at home	2137.32 (275.17)	1614.09 (207.76)	523.24	8.79	Per hour	Average hourly cost across municipalities (€57)
Community or district nurse	607.29 (100.95)	438.59 (73.00)	168.69	7.86	Per hour	Average hourly cost across municipalities (€75)
Rehabilitation§	77.75 (14.34)	53.00 (13.21)	24.75	7.77	Per hour	Average hourly cost across municipalities (€75)
<i>Medicines</i>						
No of Antibiotics	2.41 (0.13)	1.89 (0.11)	0.52	17.28	Various	Pharmacy consumer price (30)
No of R03 ATC codes (COPD medicine)	25.08 (0.68)	23.92 (0.65)	1.16	7.08	Various	Pharmacy consumer price (30)

*Standardized difference: difference between randomization group averages divided by the standard deviation of the total sample
§Incomplete register-data. Data unavailable for 4 municipality districts (2 in the control group and 2 in the intervention group, respectively)
SE = Standard error of the mean

The unadjusted within-trial costs are summarized in Table 4. The annual per patient healthcare service costs (excluding intervention costs) were higher in the telehealthcare group (by €836) driven primarily by higher costs in the municipality districts on practical help and home care as well as costs to community or district nurses. Table 4 also reveals that COPD-specific hospital admissions costs are roughly the same in the telehealthcare and usual care group. Excluding intervention costs, the three largest healthcare service cost drivers in telehealthcare were COPD-specific hospital admissions (34%), costs associated with practical help and care in municipality districts (24%) and medicine (20%). By adding intervention costs (also elaborated in Table 4), the raw mean difference in annual per patient total costs between telehealthcare and usual care was €1540.

Table 4: Average costs per patient across treatment groups at 12 months follow-up (€)				
	Mean (SE) costs		Between group difference	
Service use	Telehealthcare (n=578)	Usual care (n=647)	Raw (€)	Standardized (%)*
<i>Hospital contacts</i>				
Admissions	2756.1 (463.8)	2753.1 (458.9)	3.0	0.02
Outpatient/emergency department visits	343.4 (24.8)	278.3 (21.5)	65.1	11.37
<i>Primary care contacts</i>	602.9 (17.8)	629.4 (20.3)	-26.5	-5.55
<i>Municipality care contacts</i>				
Help and care at home	1936.7 (249.3)	1462.6 (188.2)	474.1	8.79
Community or district nurse	733.4 (121.9)	529.7 (88.1)	203.7	7.86
Rehabilitation§	93.4 (11.01)	61.0 (10.57)	32.4	8.56
<i>Medicine</i>	1610.1 (45.2)	1525.7 (37.7)	84.4	8.26
<i>Service costs (excluding intervention costs)</i>	8076.0 (417.6)	7239.8 (411.5)	836.2	5.76
Project Management	7.4	0	7.4	-
Computer hardware and peripherals	200.5	0	200.5	-
Installation	38.6	0	38.6	-
Maintenance and Support	94.6	0	94.6	-
Training healthcare professionals	12.4	0	12.4	-
Patient specific training	20.6	0	20.6	-
Monitoring vital signs	330.0 (12.76)	0	330.0	123.43
<i>Total costs (including intervention costs)</i>	8780.2 (417.2)	7239.8 (411.5)	1540.4	10.61

*Standardized difference: difference between randomization group averages divided by the standard deviation of the total sample

§Imputed data

SE = Standard error of the mean

Table 5 presents the results of the incremental analyses. The base-case adjusted average difference in QALYs was 0.0132 (not statistically significant) with an adjusted average difference in annual total costs of €728 per patient. Based on these estimates, the ICER is €55,327 per QALY. This telehealthcare solution is therefore only cost-effective if the willingness-to-pay threshold exceeds the ICER estimate. However, no threshold value exists in Denmark. Figure 1, therefore presents a cost-effectiveness acceptability curve (CEAC) and it can be seen that decision-makers should be willing to pay more than €55,000 to achieve a probability of cost-effectiveness greater than 50%.

Table 5: Incremental costs (€) and incremental QALYs at 12 months follow-up		
n=1,225 (Telehealthcare: n=578; Usual care n=647)	Between group difference (95% CI)	Intra-class coefficient (ICC)
	or ICER	
Base-case analysis		
QALY (unadjusted mean difference)*	0.0062 (-0.0307; 0.0431)	0.007
Costs (unadjusted mean difference)*	1219 (-937; 3376)	0.014
QALY (adjusted mean difference)**	0.0132 (-0.0083; 0.0346)	0.000
Costs (€) (adjusted mean difference)***	728 (-754; 2211)	0.014
ICER (adjusted, € per QALY)	55,327	
Sensitivity analysis 1: All-cause hospital contacts		
Costs (€) (adjusted mean difference)***	583 (-1397; 2563)	0.005
ICER (adjusted, € per QALY)	44,301	
Sensitivity analysis 2: Reduced procurement prices and larger scale		
Costs (€) (adjusted mean difference)***	618 (-865; 2100)	0.014
ICER (adjusted, € per QALY)	46,931	
Sensitivity analysis 3: Reduced monitoring time		
Costs (€) (adjusted mean difference)***	525 (-969; 2018)	0.012
ICER (adjusted, € per QALY)	39,854	
Sensitivity analysis 1+2+3: Most optimistic scenario		
Costs (€) (adjusted mean difference)***	277 (-1700; 2255)	0.014
ICER (adjusted, € per QALY)	21,068	

QALY: Quality adjusted life years

ICER: Incremental cost-effectiveness ratio

* Linear mixed model with treatment arm as only covariate

** Linear mixed model adjusted for treatment arm, baseline EQ5D score, baseline costs, age, baseline FEV1%, presence of musculoskeletal and clustering.

*** Linear mixed model adjusted for treatment arm, baseline EQ5D score, age, gender, baseline FEV1%, marital status, presence of diabetes, presence of cancer and clustering

Sensitivity analyses

Results from sensitivity analyses are also presented in Table 5 and CEACs for all scenarios are presented in Figure 2. In sensitivity analysis 1, all-cause hospital contacts were included in the analysis. Incremental total costs remain higher in the telehealthcare groups (€583) with an ICER of €44,301 per QALY. From Figure 2, it can be seen that the willingness-to-pay threshold falls to €45,000 per QALY to achieve a probability of cost-effectiveness greater than 50%.

By reducing procurement prices and operating on a larger scale (sensitivity analysis 2), incremental total costs falls to €618 (ICER=€46,931 per QALY). The willingness-to-pay threshold is €49,000 per QALY if a probability of cost-effectiveness greater than 50% should be achieved.

Sensitivity analysis 3 (reducing average per patient monitoring time from 5 to 2 minutes) would reduce incremental total costs to €525 and the ICER to €39,854. The willingness-to-pay threshold falls to €40,000 per QALY if a probability of cost-effectiveness greater than 50% should be achieved.

In the most optimistic scenario combining the results from all sensitivity analyses (1+2+3), the adjusted incremental costs of telehealthcare were €277 giving rise to an ICER of €21,068 per QALY and a willingness-to-pay threshold of €21,000 per QALY to achieve a probability of cost-effectiveness greater than 50%.

DISCUSSION

This study is the largest trial-based cost-utility study of telehealthcare to COPD patients in Denmark so far. The reported ICER is €55,327 per QALY which is higher than any explicit threshold values employed by countries today, e.g. those recommended in the UK (44). The cost-effectiveness conclusion is robust to changes in the definition of hospital contacts and reduced intervention costs. Only in the most optimistic scenario combining the effects of all sensitivity analyses, does the ICER fall below UK thresholds. The telehealthcare solution is therefore unlikely to be cost-effective for all included COPD patients by UK standards; however, since no threshold values exist in Denmark, it may still be cost-effective here.

Strengths and limitations

A relatively broad range of cost categories from contacts in healthcare and social services are included and these contacts are all based on register data routinely registered in Denmark. A healthcare and social sector perspective was chosen which excludes transportation costs, time spent by patients and relatives and productivity loss to society. But travel distances in Denmark are relatively short compared to other larger countries (the longest distance to a university

hospital is 160 km) and only 11% of the patients enrolled in the trial stated that they are employed (5% are full-time; 6% part-time).

The recruiting process of patients may have impacted on cost-effectiveness. Recruited COPD patients were presumably in a stable phase of their disease (no or few exacerbations and hospital admissions) at the time of inclusion, since it was required of them to show up at an appointment with their general practitioner. It is unknown if more acute patients, e.g. recruited from open hospital admissions would have changed the cost-effectiveness conclusion significantly.

The way telehealthcare was implemented may have affected cost-effectiveness. The involved organizations and healthcare professionals underwent a steep learning curve after implementation of the telehealthcare solution, where they had to find new ways of working together and adapt to new work procedures. Monitoring is one example that became much more efficient at the end of the trial, when the needs and reactions of patients as well as work tasks were more familiar to municipality healthcare personnel. Other implementation effects such as how care-coordination across municipality districts, hospitals and GPs actually occurred or the engagement of patients, health professionals and involved organizations could also have affected cost-effectiveness, but is hard to quantify post hoc.

Comparison with other studies

To our knowledge, three other studies have recently published cost-effectiveness results for telehealthcare involving COPD patients and they all demonstrated a low probability of cost-effectiveness by the standards of their countries (35,45,46). A British study (Whole System Demonstrator) concludes that telehealth as a supplement to usual care is not likely to be cost-effective for patients with COPD, diabetes and chronic heart failure primarily due to a “similar” QALY-gain and high intervention costs (35). However, this does not exclude that the COPD subgroup is cost-effective which remain to be seen. The Telescot initiative for COPD patients concludes that their telehealth initiative was associated with a non-significant QALY-gain and higher costs (45). A study based in Northern Ireland also concludes that telehealthcare is not cost-effective (46). Our findings are similar (non-significant QALY-gain and higher costs), but contrary to the UK experiences, it is not the intervention costs alone that have a considerable effect on the cost-effectiveness of telehealthcare, but rather differences in community care costs and the failure to save costs on COPD-related hospital contacts.

Implications for clinicians and decision-makers

Danish decision-makers has determined that if the telehealthcare solution in this trial proves cost-effective, it can serve as a national Danish standard for a technological platform as well as an implementation model for telehealthcare to this

patient group (47). However, the results suggest that the target COPD-population in this study may have proven to be too broad. An implication could be that decision-makers should await further research, at least into sources of heterogeneity in this trial.

It is unknown whether the telehealthcare solution has released its full potential for cost-effectiveness. E.g. in-optimal implementation could potentially have had a large impact on cost-effectiveness. It is therefore important for healthcare professionals and decision-makers to spend time learning from the experiences gained within the trial in order to investigate if any best practices could be implemented that would increase effectiveness and/or reduce cost without compromising safety and effectiveness.

Future studies

This study indicates that telehealthcare could potentially assist not only in hindering some COPD-related hospital contacts, but also hospital contacts associated with other diseases (incremental costs were reduced by applying all-cause hospital contacts). It could be a coincidence but also due to closer collaboration between healthcare delivery organizations or more frequent monitoring of physical measurements that may also be indicative of other diseases. Future studies should therefore investigate the link between telehealthcare, COPD patients with well-defined comorbidities and hospital contacts.

Average cost-effectiveness estimates applied in this and other studies could in general hide important sources of heterogeneity. Not much is known on prognostic criteria (e.g. socio-demographic-, geographic-, lifestyle- or health characteristics of the patients) for cost-effectiveness of telehealthcare to chronically ill patients, so further heterogeneity studies should be conducted and are also planned within this trial.

Telehealthcare is a complex intervention involving not only a broad class of technologies, but also organizational infrastructures, actions of healthcare professionals and patients. Future studies are needed that explicitly describe or account for the causation of the most important telehealthcare-activities that are most likely to lead to “efficient” design and deployment of telehealthcare as well as the context in which telehealthcare is implemented.

ACKNOWLEDGEMENTS

The authors would like to thank the participants for their time and effort in conducting physical measurements and completing study questionnaires. Also thanks to the North Denmark Region, the 26 municipality districts and around 344 general practitioners in the region for facilitating the implementation of the trial.

DECLARATIONS

Detailed description of intervention and comparator: The study protocol includes a detailed description of the intervention and comparator. The study protocol is freely available and can be found at <http://www.trialsjournal.com/content/15/1/178>.

Details of contributors: OH is the principal investigator for the TeleCare North trial and LHE is lead investigator for the economic evaluation in the trial; LHE and OH planned the overall trial design and are guarantors of the statistical quality for the trial as a whole. FWU and PHL contributed to the detailed planning of the data collection of trial questionnaires. FWU planned and collected register data. FWU planned and conducted all analyses under the supervision of LHE and OH. FWU reported the analyses. All authors met regularly during and after the trial period and contributed as a whole to interpreting and the presentation of the data. All authors reviewed and approved the manuscript. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding: This is an independent manuscript commissioned and jointly funded by North Denmark Region, the 26 municipality districts in North Denmark Region, The Obel Family Foundation, the Danish Agency for Digitalization Policy and Strategy, the European Social Fund and Aalborg University.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) FWU, PHL, OH and LHE have support from the North Denmark Region, the 26 municipality districts in North Denmark Region, The Obel Family Foundation, the Danish Agency for Digitalization Policy and Strategy, the European Social Fund and Aalborg University for the submitted work; (2) FWU, PHL, OH and LHE have no relationships with any organization that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) FWU, PHL, OH and LHE have no non-financial interests that may be relevant to the submitted work.

Ethical approval: The study is conducted in accordance with the Helsinki Declaration. The trial has been presented to the Regional Ethical Committee for Medical Research in the North Denmark Region where it was determined that no ethical approval was necessary. The trial has also been authorized by the Danish Data Protection Agency. All patients signed an informed consent form before taking part in the clinical trial.

Data sharing: No additional data available

Transparency: OH and LHE affirm that the manuscript is an honest, accurate, and transparent account of the study being reported and no important aspects of the study have been omitted.

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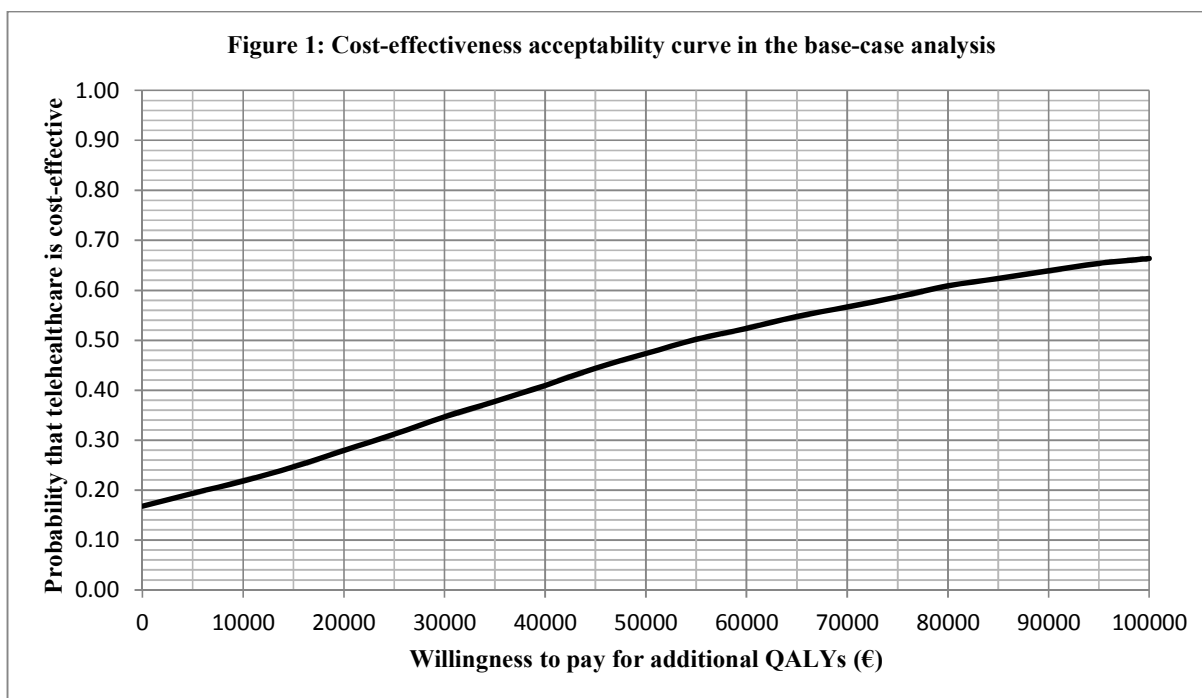
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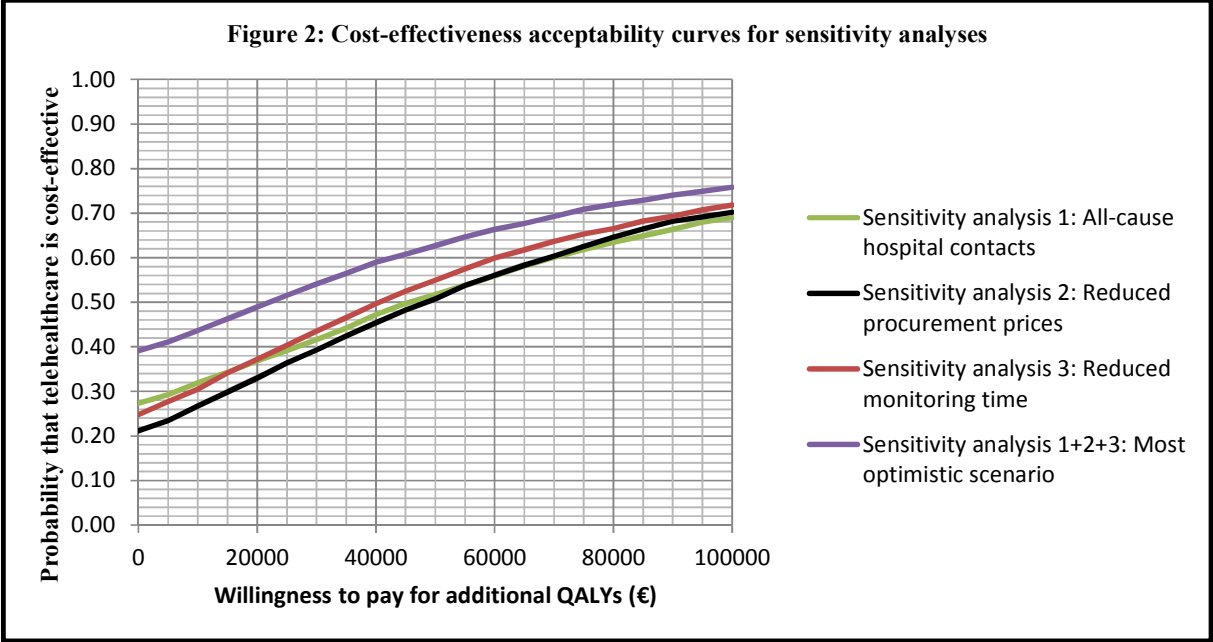
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Additional file 1

Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Checklist
Items to include when reporting economic evaluations of health interventions

Section/Topic	Item No	Recommendation	Reported on page No / Line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	P1, L1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	P2, L1-23
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Study protocol P4, L1-16
		Present the study question and its relevance for health policy or practice decisions.	Study protocol P4, L16-19
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Study protocol Table 2
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Study protocol P2, L5 P12, L27-28 P13, L1
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Study protocol P2, L13 P4, L1-2 P5, L3
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Study protocol Table 1
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Study protocol P2, L4 P5, L2
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	P7, L28 – P8, L2
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Study protocol P5, L2 P9, L9-11

Measurement of effectiveness	11a	<i>Single study-based estimates:</i> Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Study protocol
	11b	<i>Synthesis-based estimates:</i> Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	N/A
Measurement and valuation of preference-based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	N/A
Estimating resources and costs	13a	<i>Single study-based economic evaluation:</i> Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	P6, L1 to P8, L7
	13b	<i>Model-based economic evaluation:</i> Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	N/A
Currency, price data, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	P8, L3
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	N/A
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	N/A
Analytic methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	P8, L16 to P10, L26
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 2 Table 3 Table 4
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 5
Characterizing uncertainty	20a	<i>Single study-based economic evaluation:</i> Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	Table 5 Figure 1 Figure 2 P15, L1-L14
	20b	<i>Model-based economic evaluation:</i> Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	N/A
Characterizing heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	N/A
Discussion			
Study findings, limitations,	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	P15, L15-P17 end

generalizability, and current knowledge			
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	P18
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	P18

BMJ Open

Cost-effectiveness of telehealthcare to patients with chronic obstructive pulmonary disease: Results from the Danish "TeleCare North" cluster-randomized trial.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-014616.R1
Article Type:	Research
Date Submitted by the Author:	11-Mar-2017
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Primary Subject Heading:	Health economics
Secondary Subject Heading:	Health policy, Medical management, Patient-centred medicine
Keywords:	BIOTECHNOLOGY & BIOINFORMATICS, Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS, HEALTH ECONOMICS

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Cost-effectiveness of telehealthcare to patients with chronic obstructive pulmonary disease: Results from the Danish “TeleCare North” cluster-randomized trial

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ABSTRACT

Objectives: To investigate the cost-effectiveness of a telehealthcare solution in addition to usual care compared with usual care.

Design: A 12 month cost-utility analysis conducted alongside a cluster-randomized trial.

Setting: Community based setting in the geographical area of North Denmark Region in Denmark.

Participants: 26 municipality districts define randomization clusters with 13 districts in each arm. 1,225 patients with chronic obstructive pulmonary disease were enrolled of which 578 patients were randomized to telehealthcare and 647 to usual care.

Interventions: In addition to usual care, patients in the intervention group received a set of telehealthcare equipment and were monitored by a municipality-based healthcare team. Patients in the control group received usual care.

Main outcome measure: Incremental costs per quality-adjusted life-years gained from baseline up to 12 months follow-up.

Results: From a healthcare and social sector perspective, the adjusted mean difference in total costs between telehealthcare and usual care was €728 (95% CI: -754; 2211) and the adjusted mean difference in quality-adjusted life-years gained was 0.0132 (95% CI: -0.0083; 0.0346). The incremental cost-effectiveness ratio was €55,327 per quality-adjusted life-year gained. Decision-makers should be willing to pay more than €55,000 to achieve a probability of cost-effectiveness greater than 50%. This conclusion is robust to changes in the definition of hospital contacts and reduced intervention costs. Only in the most optimistic scenario combining the effects of all sensitivity analyses, does the incremental cost-effectiveness ratio fall below UK thresholds values (€21,068 per quality-adjusted life-year).

Conclusions: Telehealthcare is unlikely to be a cost-effective addition to usual care if it is offered to all patients with chronic obstructive pulmonary disease and if the willingness-to-pay threshold values from National Institute for Health and Care Excellence are applied.

Trial registration: Clinicaltrials.gov, NCT01984840, November 14, 2013.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study reports the within-trial cost-effectiveness of a pragmatic large-scale asynchronous telehealthcare initiative in order to improve the international evidence base of the economic effects of telehealthcare for COPD patients.
- A relatively broad health care and social sector perspective was chosen and the cost-analyses of resource use are based on register data.
- A limitation of the study is that only 61% of the participants had complete registrations of all cost-categories and outcomes.
- The way telehealthcare was implemented may have affected cost-effectiveness, since the involved organizations and healthcare professionals underwent a steep learning curve after implementation of the telehealthcare solution, where they had to find new ways of working together and adapt to new work procedures.

Keywords: RCT; Telehealth; Telecare; Telemonitoring; COPD; Economic Evaluation; Cost-effectiveness; Denmark

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease (1). The main symptoms of COPD are dyspnea, recurrent lung infections, abnormal sputum, wheezing, decreased exercise tolerance and “smoker’s cough” (2). Depending on the severity of COPD, patients can experience a number of exacerbations, where symptoms become more severe than normal, which are often associated with a further progression of the disease (2) and anxiety (3). COPD is one of the most prevalent and deadly diseases in the world (4). The global prevalence of COPD is high (11,7%) (5). COPD is associated with high mortality (6), presence of comorbidities (7,8) and reduced health-related quality-of-life (9,10). COPD poses a substantial financial burden on healthcare systems, e.g. the annual direct costs for COPD has been estimated to \$20-26 billion in the US with hospital admissions representing 52-70% of all direct costs (11). A recent Danish study has estimated that COPD is responsible for 8,300 years of life lost and €174 million in annual direct cost for treatment and care (12).

Telehealthcare has been suggested as a possible effective intervention to patients with COPD on especially health-related quality-of-life (13). Telehealthcare is a technology that contains data from a patient which is transferred electronically over a physical distance and healthcare professionals exercise their judgment in providing personalized feedback to the patient based on these data (14). Some feasibility studies including cost-analyses have previously suggested an added value of telehealthcare compared to usual practice and some of these studies show that telehealthcare may lower hospital or healthcare costs (15–19). But most recent systematic reviews have questioned the quality of this evidence and have requested more cost-effectiveness evaluations (20–24), preferably with broader cost-perspectives (25).

The objective of this paper is to add to this international evidence base on the cost-effectiveness of telehealthcare by presenting the results of a cost-utility analysis of a telehealthcare intervention to patients with COPD compared with usual practice. The analysis was nested within a 12-months cluster-randomized trial (called “TeleCare North”) that were conducted in the geographic area of North Denmark Region in Denmark from 2013-2014.

METHODS

A more detailed trial protocol has been published elsewhere (26), but a brief summary is provided in Table 1. 26 municipality districts in North Denmark Region define the randomization clusters with 13 districts in each arm. In addition to usual care, patients in the intervention group received a set of telehealthcare equipment and were monitored by a community-based healthcare team. Patients in the control received usual care.

Table 1: Description of the Danish TeleCare North cluster-randomized trial	
Eligible criteria for clusters	All municipalities in North Denmark Region except one (a small island off the coast), 10 municipalities in all. Each municipality consisted of between 2 and 5 municipality districts and these districts were randomization units, 26 municipality districts in total (13 in each arm).
Eligible criteria for patients	COPD as primary disease, diagnosis by spirometry, in treatment according to guidelines recommended by “The Global Initiative for Chronic Obstructive Lung Disease (GOLD)” (1), at least two exacerbations within the past 12 months, motivated for treatment, fixed residence in North Denmark Region, The Modified Medical Research Council scale (mMRC) ≥ 2 or mMRC ≥ 3 and COPD Assessment Test (CAT) ≥ 10 . Exclusion criteria were: no phone line or Global System for Mobile communications (GSM) coverage, unable to understand Danish sufficiently to complete the study questionnaires or diagnosed with a cognitive impairment.
Intervention group: Cluster-level intervention	Municipality district healthcare personnel (primarily nurses and health assistants) were trained in two separate sessions. One session focused on the technical aspects of the tablet and physical measurements. Another session focuses on general disease awareness and communication with patients. The training was performed by members of the trial administration office. General practitioners were responsible for establishing threshold values for physical measurements. Nurses in the patient’s residing municipality were responsible for monitoring the data obtained and should incorporate monitoring time duties with their existing job responsibilities. Exemptions were COPD patients receiving oxygen therapy and COPD patients with open hospital admissions who were monitored at their hospital as usual. Patients were monitored asynchronously by a nurse on a daily basis. Measurements were classified with either a green, yellow or red code (Green code: no threshold values were exceeded. Yellow code: one or more values exceeded the threshold values. Red code: one or more values exceeded the threshold values and had not previously been recorded). The nurse had the option to contact the patient by telephone and/or the patient’s general practitioner and/or dispatch an ambulance. Installation, swopping of defects, de-installation and technical support and maintenance of the equipment was handled by IT-specialists.
Intervention group: Patient-level intervention	Telephone contact to each patient from municipality healthcare personnel no later than 10 days after randomization, and a 45-minute appointment scheduled for patients who wanted to receive the tablet at home. For those who wished to receive the tablet at a municipality health center, a 75-minute appointment was scheduled with 3 to 4 patients in each group. At both appointments, a nurse from the patients’ municipalities demonstrated the use of the tablet and instructed patients in how to conduct physical measurement. Patients were asked to measure their vital signs daily during the first two weeks (both weekdays and weekends) and 1 to 2 times weekly after the two first weeks. A 45-minute follow-up visit was scheduled 3 to 4 weeks after the first appointment to check if the patient used the device appropriately and if the threshold values of the physical measurements needed to be adjusted.
Intervention group: Device	All patients received the same device and peripherals. It consisted of a standard tablet (Samsung Galaxy) containing information on handling COPD in general and software (two apps) that automatically instructs the patient in handling COPD during exacerbations. The tablet can collect and wirelessly transmit data on blood pressure, pulse, blood oxygen saturation, and weight via an attached Fingertip Pulse Oximeter, a Digital Blood Pressure Monitor, and a scale.
Control group: Usual Care	Usual practice for caring for patients with COPD is the responsibility of the patient’s general practitioner (treatment and monitoring) and the municipalities (practical help and home nursing care). COPD patients can make appointments with their general practitioner or call the emergency contact number without copayment in order to get treatment or advice in managing COPD but this advice is not personalized. Community care administered by municipality district personnel comes at regular intervals based on a clinically based estimate of the patients’ needs, but these personnel are not necessarily certified nurses and often not fully educated in COPD and not on call.

The primary outcome measure for the cost-effectiveness analysis was the incremental cost-effectiveness ratio (ICER) expressed as the total cost per quality-adjusted life-year (QALY) gained measured from baseline to follow-up at 12 months. In defining the total costs, this trial adopted a healthcare and social care sector perspective (including hospital services, primary care, medicine, home care services and rehabilitation).

Healthcare service use and healthcare costs

Healthcare and social care service use were all estimated based on register data by applying a unique civil registration number that all Danish citizens have and that makes precise linkage between registers possible. National patient-level data for all hospital contacts were collected from the Danish National Patient Register (27), which contains all inpatient, outpatient and emergency ward visits in Denmark. The total costs for each contact is a variable in these datasets and are valued based on the diagnose-related group (DRG), the actual procedures conducted and the duration of the contact (28). The included admissions, outpatient and emergency ward visits were in the main analysis restricted to those defined as COPD-specific in the Danish Register for COPD (29).

All contacts between patients and the primary care sector were collected from the National Health Insurance Service Register (30). The costs for each contact is part of the dataset and are valued based on fees negotiated in a collective agreement (31). At present, it is not possible to identify the cause of contact to the primary care sector, so all contacts are included.

Medication use was taken from The Danish Register of Medicinal Product Statistics that contains information about what prescribed medicine citizens purchase in Denmark (32). For this analysis these are restricted to patient-level medicine associated with COPD (R03 ATC codes), specific antibiotics, antifungals and medicine for anxiety, all associated with the treatment of COPD-exacerbations, as well as medicine for smoking cessation. The costs for each product is given in this dataset and is valued based on a standardized pharmacy consumer price (33).

Patient-level community care service use was collected from individual care systems in each of the 26 included municipality districts. The type and duration of standard care activities such as personal care, practical help, home nursing care and rehabilitation activities are routinely recorded for each contact. Each municipality district values contacts differently based on an internal calculated mean hourly cost. It was pragmatically decided to value time consumption in municipality districts as an average of the reported hourly costs from municipality districts. Four of the 26 municipality districts in the trial were implementing a different IT-system at the time of data collection which meant that rehabilitation costs for these four municipality districts were unavailable (2 municipality districts in the telehealthcare group and 2 in the usual care group).

Healthcare service use was collected for 12-months to allow for within-trial costs to be calculated. In addition, patient-level health service use was also collected 12 months prior to randomization, because it was suspected that baseline

differences in costs could occur that would not be explained by differences in health status or socio-demographic characteristics by patients, e.g. due to variations in referral and visitation practices across municipality districts.

Intervention costs

Costs associated only with the clinical trial, preparing the organization and developing the telehealthcare solution were excluded. Intervention costs were costs of hardware and peripherals, installation and deinstallation costs, maintenance and support costs, training costs for healthcare professionals, patient specific training, monitoring costs and project management costs.

Per person costs of the “package” of telehealthcare equipment (the so-called “Telekits” consisting of a tablet and peripherals) were calculated. The “Telekits” supplied were exactly the same for all patients and was purchased to each patient ahead of the trial and valued as prices paid. The per person costs of installation/deinstallation and swapping any defects in the equipment was negotiated with an external supplier prior to the trial and valued as prices paid. Per patient maintenance and support costs consisted of software licenses and data charges, technical support to patients and healthcare professionals as well as IT-infrastructure- and application maintenance and valued as prices paid. Costs associated with IT-infrastructure- and application maintenance was not dependent on the number of patients in the trial but the software and hardware configuration employed by the telehealthcare solution which in principle could include all COPD patients and patients with chronic heart failure. It was decided to allocate these costs on the estimated number of COPD and chronic heart failure patients in North Denmark Region (10,500 patients) (34,35). The per patient costs of training healthcare professionals were based on planned time spent conducting education workshops in COPD disease awareness and the telehealthcare solution, the number of conducted workshops and the average hourly wage for a community district nurse. Per patient costs of patient specific training were based on planned time and valued based on a mean hourly wage for a community district nurse. Time spent per patient on monitoring were estimated by time registries in the municipality districts and valued based on a mean hourly wage for a community district nurse. Based on the experiences gained with the implementation in the trial period, it was estimated that it would be necessary to have an administrative officer employed to “run” the telehealthcare solution, should it be implemented in routine practice (coordinating activities, contract supervision etc.). Project management costs were valued as mean yearly salary for an administrative officer including all standardly available pensions and pay supplements (36). As with IT-infrastructure- and application maintenance, these costs could be allocated on more patients than in the trial and they were therefore

also allocated on the estimated number of COPD and chronic heart failure patients in North Denmark Region (10,500 patients) (34,35).

Equipment costs (the Telekits), installation/deinstallation costs, costs associated with training healthcare professionals and patient specific training were annuitized over a period of five years with a discount rate of 3% p.a. and presented as equivalent annual cost. 5 years and 3% can be used as standard lifetime and discount rate for “other IT-equipment” in Danish capital accounting (37).

All costs are reported in 2014 prices. Costs were obtained in Danish kroner (DKK) and exchanged to Euro (€) using the average 2014 exchange rate (1€ = 7.4547DKK). All healthcare service use and costs are reported as means and standard errors and where descriptive statistics are presented, differences between intervention and control group means are reported as raw differences and, to allow for future meta-analysis, as standardized differences (the raw difference between group means, divided by the standard deviation of the total sample) presented as a percentage.

Effectiveness

Information of mortalities were obtained from the Danish Register of Causes of Death (38) which contain mortality statistics on all deaths in Denmark. Utility scores stem from the EQ5D-3L health-related quality-of-life questionnaire with Danish societal weights (39). QALYs were calculated by linear interpolation of utility scores. The health-related quality-of-life items and relevant demographic data were collected at baseline by help from the patients’ general practitioners who distributed the questionnaires to all patients but with a prepaid return envelope to the trial administration office. At follow-up, a questionnaire consisting of the health-related quality-of-life items were sent from the trial administration office to the patients’ home addresses with a prepaid return envelope.

ANALYSIS

Statistical analyses were all performed in STATA version 12.1 except the probabilistic sensitivity analysis that was developed in Microsoft Excel 2010.

Missing data

1,225 patients were randomized in the study (578 patients in the telehealthcare group and 647 in the control group). At baseline, missing data for the EQ5D summary score were present for 8% of the participants (48 in the telehealthcare group; 53 in the control group). 103 patients died during the trial period (8%; 50 in telehealthcare group; 53 in control group) and they were assigned an EQ5D summary-score of 0 at follow-up that were used in the QALY calculation (40). In addition, 27% had missing data on the EQ5D summary score at follow-up (199 in the telehealthcare group; 133 in the

control group) either due to non-response or to incomplete registration of EQ5D questionnaire items. 12% had missing values on rehabilitation costs (79 in the telehealthcare group; 73 in the control group). Complete data for both total costs (i.e. all cost-categories), baseline EQ5D-score and EQ5D-score at follow-up were available for 751 patients (61%; 325 in telehealthcare group; 426 in control group).

Current good practice for trial-based economic evaluation recommends that analyses should account for missing data by imputation, especially when there is a large amount of missing data (41). The applied imputation procedure followed the principles recommended by Faria and colleagues (42). Missing data were assumed missing at random (MAR), which can be a plausible assumption if a wide range of variables, and variables that are predictive of missingness, are included in the imputation model (43). Therefore, missing data on EQ5D scores, rehabilitation costs and baseline characteristics were imputed using the *mi impute chained* command in STATA12.1 and 30 complete datasets were created. Continuous variables were imputed by predictive mean matching and categorical variables by multinomial logistic or logistic regression. Imputation models included outcome variables, predictors for the outcomes at both time points and predictors for missing observations in the individual variables. The imputation models were estimated separately by treatment group and included the clustering variable, measures of health-related quality-of-life (EQ5D scores), costs at baseline or at 12 months follow-up (in the categories presented in Table 4), measures of disease status (forced expiratory volume in one second (FEV1%), forced vital capacity (FVC%), diastolic- and systolic blood pressure), smoking status, presence of comorbidities (diabetes, cancer, cardiovascular disease, mental illness or musculoskeletal disorders) and socio-demographic variables (age, gender, marital status, education and employment status).

Cost-effectiveness analysis

The cost-effectiveness analysis followed an intention-to-treat principle. The statistical analysis applied multilevel modeling for continuous variables that rely on near-normality (44), which has been suggested as an analysis strategy for cost-effectiveness research of cluster-randomized trials (45). To allow for different sets of covariates, estimation of incremental total costs and incremental QALYs gained was based on two separate linear mixed effects models; one for total costs and one for QALYs. Total costs were controlled for treatment arm, baseline EQ5D score, baseline costs (total costs 12 months prior to randomization), age, baseline FEV1%, presence of musculoskeletal disease (a significant cost driver in municipality districts) and clustering. QALYs gained were controlled for treatment group, baseline EQ5D score, age, gender, baseline FEV1%, marital status, presence of diabetes, presence of cancer and clustering. These

estimations were facilitated by the *mi estimate: xtmixed* command with robust standard errors. A deterministic ICER-estimate was calculated using the treatment beta-coefficients from these two models. In order to explore the uncertainty surrounding cost-effectiveness, the output from the *mi estimate: xtmixed* was exported to Microsoft Excel 2010 along with Cholesky's decomposition matrix to allow for a potential correlation between all the parameters in the analyses models. By redrawing new parameter estimates from the estimated treatment-effect with its standard error, 5,000 simulations were calculated to obtain new estimates of incremental QALYs and incremental total costs which were used to construct cost-effectiveness acceptability curves.

Sensitivity analysis 1: All-cause hospital contacts

In the base-case analysis, we have sought to limit hospital contacts to COPD-specific contacts because the hypothesis were that telehealthcare could prevent a proportion of admissions and emergency ward visits associated with exacerbations and make most COPD-specific outpatient control visits redundant. However, it became apparent that the included patients suffer from a variety of diseases concomitant with COPD (see Table 2). As part of the intervention, it is therefore plausible that a more integrated care and monitoring approach assisted by the telehealthcare technology could also prevent some hospital contacts due to comorbidities. Some of the measurements facilitated by the Telekits could e.g. be indicative of cardiovascular disease and especially chronic heart failure. The effect on incremental costs of including all hospital contacts was therefore explored.

Sensitivity analysis 2: Reduced procurement prices and larger scale

Potential discounts on procurement prices could be achieved when contemplating to implement technologies on a larger scale and increased capacity of the telehealthcare solution could also drastically reduce intervention cost thereby affecting the cost-effectiveness conclusion. Therefore, an effect of a 30% discount on Telekit equipment, installation, support and maintenance was explored. 30% is an estimate stemming from experiences with negotiating procurement prices subject to large-scale implementation of telehealthcare in the Danish healthcare sector (46). In addition, suppliers have stated that the costs of maintenance (IT-infrastructure and applications) and support costs does not depend on the number of patients included, but the complexity of the hardware and software configuration. The effects of making these costs negligible due to very large-scale implementation were therefore also explored.

Sensitivity analysis 3: Reduced monitoring time

Municipality healthcare personnel had a steep learning curve for their new monitoring tasks and the patients' need for monitoring was uncertain at the outset. This resulted in approximately 5 minutes of average monitoring time per patient

per week in the trial. After 12 months, personnel had become more efficient at monitoring and responding to vital values, so a new average target of 2 minutes per week per patient (i.e. 110 minutes annually) have been discussed by the North Denmark Region and the municipality districts (47) and the effects of this target on cost-effectiveness is investigated.

Finally, a most optimistic scenario exploring the combined effect of sensitivity analyses 1, 2 and 3 was investigated. The effect on total costs and/or QALYs was explored using the same models and covariates as the base-case analysis.

RESULTS

Baseline characteristics of all the included patients are presented in Table 2. Baseline characteristics are fairly balanced across treatment groups. The FVC(%) is lower in the telehealthcare group and there is an overall tendency for patients in the telehealthcare group to have slightly worse health (lower average lung function, lower average health-related quality of life, higher average proportion of comorbidities (except musculoskeletal disorders)). The number of smokers is higher in the intervention arm and baseline costs were also higher in the telehealthcare group.

Table 2: Baseline characteristics			
	All 1,225 participants at baseline		
	Telehealthcare	Usual care	Difference
	n=578	n=647	Raw
Age (years)§	69.55 (9.36)	70.33 (9.11)	-0.78
Men (%)§	48.27 (n=279)	43.74 (n=283)	4.53
Marital status (%)			
Married/In a relationship	55.88 (n=323)	54.25 (n=351)	1.63
Single	20.42 (n=118)	22.10 (n=143)	-1.68
Widow/Widower	16.78 (n=97)	16.54 (n=107)	0.24
Missing (%)	6.92 (n=40)	7.11 (n=46)	-0.19
Smoking status (%)			
Non-smokers	59.34 (n=343)	63.06 (n=408)	-3.72
Smokers	33.91 (n=196)	29.21 (n=189)	4.70
Missing (%)	6.75 (n=39)	7.73 (n=50)	-0.98
Duration of COPD (years)	7.80 (6.23)	7.70 (5.79)	0.10
Missing (%)	14.01 (n=81)	15.14 (n=98)	-1.13
FEV1(%)	47.70 (18.05)	48.37 (18.94)	-0.67
Missing (%)	18.51 (n=107)	19.78 (n=128)	-1.27
FVC(%)	70.38 (20.02)	74.34 (22.33)	-3.96
Missing (%)	34.43 (n=199)	39.41 (n=255)	-4.98
Comorbidities (%)			
Diabetes	10.21 (n=59)	9.89 (n=64)	0.32
Coronary heart disease	32.70 (n=189)	31.84 (n=206)	0.86

Mental health problem	4.84 (n=28)	4.79 (n=31)	0.05
Musculoskeletal disorder	24.91 (n=144)	29.37 (n=190)	-4.46
Cancer	6.06 (n=35)	4.79 (n=31)	1.27
Missing (%)	8.13 (n=47)	7.88 (n=51)	0.25
Baseline total costs (€)\$	6492 (14150)	4900 (7149)	1592
Missing (%)	13.66 (n=79)	11.28 (n=73)	2.38
Baseline EQ5D	0.706 (0.202)	0.716 (0.185)	-0.010
Missing (%)	8.30 (n=48)	8.19 (n=53)	0.11

Data are mean (standard deviation) or proportion (number of patients)

COPD: chronic obstructive pulmonary disease; FEV1(%): forced expiratory volume in one second of predicted normal;

FVC(%): forced vital capacity

\$Variable has no missing values

\$Baseline total costs are missing for 3 cost categories (Help and care at home, Community or district nurse and Rehabilitation, see Table 4) in 4 municipality districts

The unadjusted healthcare service use over the trial period with unit costs sources is summarized in Table 3. Average values for healthcare service use were not imputed (i.e. values are based on non-missing cases unadjusted for patient case mix). Table 3 reveals that resource use is consistently higher in the telehealthcare group.

Table 3: Service use at 12 months across treatment groups and applied unit costs						
	Mean (SE) contacts		Between group difference		Unit	Unit cost
Service use	Telehealthcare (n=578)	Usual care (n=647)	Raw	Standardized (%)*		
<i>Hospital contacts</i>						
Admissions	0.5 (0.05)	0.45 (0.49)	0.046	3.70	Per contact	DRG value of contact (28)
Inpatient bed days	2.69 (0.31)	2.60 (0.31)	0.09	1.18	Per contact	Included in DRG value of contact (28)
Outpatient/emergency department visits	0.87 (0.08)	0.74 (0.07)	0.13	7.16	Per contact	DRG value of contact (28)
<i>Primary care contacts</i>						
General practitioner	10.72 (0.35)	9.92 (0.33)	0.80	9.35	Per contact	Tariffs from Collective agreement (31)
<i>Municipality care (time spent)</i>						
Help and care at home	2137.32 (275.17)	1614.09 (207.76)	523.24	8.79	Per hour	Average hourly cost across municipalities (€57)
Community or district nurse	607.29 (100.95)	438.59 (73.00)	168.69	7.86	Per hour	Average hourly cost across municipalities (€75)
Rehabilitation§	77.75 (14.34)	53.00 (13.21)	24.75	7.77	Per hour	Average hourly cost across municipalities (€75)

<i>Medicines</i>						
No of Antibiotics	2.41 (0.13)	1.89 (0.11)	0.52	17.28	Various	Pharmacy consumer price (33)
No of R03 ATC codes (COPD medicine)	25.08 (0.68)	23.92 (0.65)	1.16	7.08	Various	Pharmacy consumer price (33)

*Standardized difference: difference between randomization group averages divided by the standard deviation of the total sample
§Incomplete register-data. Data unavailable for 4 municipality districts (2 in the control group and 2 in the intervention group, respectively)
SE = Standard error of the mean

The unadjusted within-trial costs are summarized in Table 4. The annual per patient healthcare service costs (excluding intervention costs) were higher in the telehealthcare group (by €836) driven primarily by higher costs in the municipality districts on practical help and home care as well as costs to community or district nurses. Table 4 also reveals that COPD-specific hospital admissions costs are roughly the same in the telehealthcare and usual care group. Excluding intervention costs, the three largest healthcare service cost drivers in telehealthcare were COPD-specific hospital admissions (34%), costs associated with practical help and care in municipality districts (24%) and medicine (20%). By adding intervention costs (also elaborated in Table 4), the raw mean difference in annual per patient total costs between telehealthcare and usual care was €1540.

Table 4: Average costs per patient across treatment groups at 12 months follow-up (€)				
Service use	Mean (SE) costs		Between group difference	
	Telehealthcare (n=578)	Usual care (n=647)	Raw (€)	Standardized (%)*
<i>Hospital contacts</i>				
Admissions	2756.1 (463.8)	2753.1 (458.9)	3.0	0.02
Outpatient/emergency department visits	343.4 (24.8)	278.3 (21.5)	65.1	11.37
<i>Primary care contacts</i>	602.9 (17.8)	629.4 (20.3)	-26.5	-5.55
<i>Municipality care contacts</i>				
Help and care at home	1936.7 (249.3)	1462.6 (188.2)	474.1	8.79
Community or district nurse	733.4 (121.9)	529.7 (88.1)	203.7	7.86
Rehabilitation§	93.4 (11.01)	61.0 (10.57)	32.4	8.56
<i>Medicine</i>	1610.1 (45.2)	1525.7 (37.7)	84.4	8.26
<i>Service costs (excluding intervention costs)</i>	8076.0 (417.6)	7239.8 (411.5)	836.2	5.76
Project Management	7.4	0	7.4	-
Computer hardware and peripherals	200.5	0	200.5	-
Installation	38.6	0	38.6	-
Maintenance and Support	94.6	0	94.6	-
Training healthcare professionals	12.4	0	12.4	-

Patient specific training	20.6	0	20.6	-
Monitoring vital signs	330.0 (12.76)	0	330.0	123.43
<i>Total costs (including intervention costs)</i>	<i>8780.2 (417.2)</i>	<i>7239.8 (411.5)</i>	<i>1540.4</i>	<i>10.61</i>

*Standardized difference: difference between randomization group averages divided by the standard deviation of the total sample

§Imputed data

SE = Standard error of the mean

Table 5 presents the results of the incremental analyses. The base-case unadjusted average difference in QALYs was 0.0062 (not statistically significant) and the unadjusted difference in total costs was €1219 per patient. The base-case adjusted average difference in QALYs was 0.0132 (not statistically significant) with an adjusted average difference in annual total costs of €728 per patient. Based on these estimates, the ICER is €55,327 per QALY. This telehealthcare solution is therefore only cost-effective if the willingness-to-pay threshold exceeds the ICER estimate.. Figure 1 presents the cost-effectiveness acceptability curve (CEAC) and it can be seen that decision-makers should be willing to pay more than €55,000 to achieve a probability of cost-effectiveness greater than 50%.

Table 5: Incremental costs (€) and incremental QALYs at 12 months follow-up		
n=1,225 (Telehealthcare: n=578; Usual care n=647)	Between group difference (95% CI)	Intra-class coefficient (ICC)
	or ICER	
Base-case analysis		
QALY (unadjusted mean difference)*	0.0062 (-0.0307; 0.0431)	0.007
Costs (unadjusted mean difference)*	1219 (-937; 3376)	0.014
QALY (adjusted mean difference)**	0.0132 (-0.0083; 0.0346)	0.000
Costs (€) (adjusted mean difference)***	728 (-754; 2211)	0.014
ICER (adjusted, € per QALY)	55,327	
Sensitivity analysis 1: All-cause hospital contacts		
Costs (€) (adjusted mean difference)***	583 (-1397; 2563)	0.005
ICER (adjusted, € per QALY)	44,301	
Sensitivity analysis 2: Reduced procurement prices and larger scale		
Costs (€) (adjusted mean difference)***	618 (-865; 2100)	0.014
ICER (adjusted, € per QALY)	46,931	
Sensitivity analysis 3: Reduced monitoring time		
Costs (€) (adjusted mean difference)***	525 (-969; 2018)	0.012
ICER (adjusted, € per QALY)	39,854	
Sensitivity analysis 1+2+3: Most optimistic scenario		
Costs (€) (adjusted mean difference)***	277 (-1700; 2255)	0.014
ICER (adjusted, € per QALY)	21,068	

QALY: Quality adjusted life years

ICER: Incremental cost-effectiveness ratio

* Linear mixed model with treatment arm as only covariate
** Linear mixed model adjusted for treatment arm, baseline EQ5D score, age, gender, baseline FEV1%, marital status, presence of diabetes, presence of cancer and clustering
*** Linear mixed model adjusted for treatment arm, baseline EQ5D score, baseline costs, age, baseline FEV1%, presence of musculoskeletal and clustering.

Sensitivity analyses

Results from sensitivity analyses are also presented in Table 5 and CEACs for all scenarios are presented in Figure 2. In sensitivity analysis 1, all-cause hospital contacts were included in the analysis. Incremental total costs remain higher in the telehealthcare groups (€583) with an ICER of €44,301 per QALY. From Figure 2, it can be seen that the willingness-to-pay threshold falls to €45,000 per QALY to achieve a probability of cost-effectiveness greater than 50%. By reducing procurement prices and operating on a larger scale (sensitivity analysis 2), incremental total costs falls to €618 (ICER=€46,931 per QALY). The willingness-to-pay threshold is €49,000 per QALY if a probability of cost-effectiveness greater than 50% should be achieved. Sensitivity analysis 3 (reducing average per patient monitoring time from 5 to 2 minutes) would reduce incremental total costs to €525 and the ICER to €39,854. The willingness-to-pay threshold falls to €40,000 per QALY if a probability of cost-effectiveness greater than 50% should be achieved. In the most optimistic scenario combining the results from all sensitivity analyses (1+2+3), the adjusted incremental costs of telehealthcare were €277 giving rise to an ICER of €21,068 per QALY and a willingness-to-pay threshold of €21,000 per QALY to achieve a probability of cost-effectiveness greater than 50%.

DISCUSSION

The adjusted mean difference in QALYs was 0.0132 (-0.0083; 0.0346) and the adjusted mean difference in costs were €728 (-754; 2211) leading to an ICER of €55,327 per QALY. This ICER is higher than any explicit threshold values employed by countries today, e.g. those recommended in the UK (48). The cost-effectiveness conclusion is robust to changes in the definition of hospital contacts and reduced intervention costs. Only in the most optimistic scenario combining the effects of all sensitivity analyses, does the ICER fall below UK thresholds. The telehealthcare solution is therefore unlikely to be cost-effective for all included COPD patients.

Strengths and limitations

This study is the largest trial-based cost-utility study of telehealthcare to COPD patients in Denmark so far. A relatively broad range of cost categories from contacts in healthcare and social services are included and these contacts are all based on register data routinely registered in Denmark. A healthcare and social sector perspective was chosen which excludes transportation costs, time spent by patients and relatives and productivity loss to society. But travel distances in Denmark are relatively short compared to other larger countries (the longest distance to a university hospital is 160 km) and only 11% of the patients enrolled in the trial stated that they are employed (5% are full-time; 6% part-time).

Data on each monitoring contact was available for 21 of the 26 municipality districts included (the remaining 5 districts has reported aggregated time spent monitoring each participant during the trial-period). The median number of monitoring encounters within these 21 districts was 53 out of 64 planned contacts (26). Although monitoring does not represent all facets of adherence and we do not have complete data for each individual encounter, it does suggest that participants in general were willing to engage with the TeleCare North initiative.

A limitation of the study is that single-level multiple imputation with clustering as a fixed effect was performed. Gomes et. al. has found that an imputation approach that account for clustering as a random effect perform better than single-level imputation (49). More specifically, Andridge have in a simulation study found that including clustering as a fixed effect in the imputation model could overestimate the uncertainty of the estimates, especially if the number of clusters are small and the ICC is low as in this case (50). However, a barrier to the adoption of multi-level multiple imputation is that these techniques are not part of conventional statistical software. Furthermore, separate modeling of costs and effects were performed in the analyses of incremental QALYs and costs, which could be less statistically efficient than joint modeling (51), although a multiway sensitivity analysis in a simulated cost-effectiveness study of bivariate multilevel models set to small correlations between costs and outcomes also perform reasonably well under the circumstances of this trial (e.g. a small number of clusters and unequal cluster sizes) (52).

Smoking status is an important risk factor for COPD (53) and the proportion of non-smokers was lower in the intervention arm, which was not accounted for in the randomization (e.g. through minimization). However, the difference in smoking status between intervention and control group is not statistically significant (Fisher's exact test, p-value=0.103) and including smoking status as an additional covariate in the QALY and cost models have little impact on treatment effects (i.e. incremental QALYs is reduced from 0.01316 to 0.01288 with smoking status included and incremental costs is changed from €728 to €705).

The way telehealthcare was implemented may have affected cost-effectiveness. The involved organizations and healthcare professionals underwent a steep learning curve after implementation of the telehealthcare solution, where they had to find new ways of working together and adapt to new work procedures. Monitoring is one example and personnel became more efficient at the end of the trial, when the needs and reactions of patients as well as work tasks were more familiar to municipality healthcare personnel. Other implementation effects such as how care-coordination across municipality districts, hospitals and GPs actually occurred or the engagement of health professionals and involved organizations could also have affected cost-effectiveness, but is hard to quantify post hoc.

Comparison with other studies

To our knowledge, three other studies have recently published cost-effectiveness results for telehealthcare involving COPD patients and they all demonstrated a low probability of cost-effectiveness by the standards of their countries (54–56). A British study (Whole System Demonstrator) concludes that telehealth as a supplement to usual care is not likely to be cost-effective for patients with COPD, diabetes and chronic heart failure primarily due to a “similar” QALY-gain and high intervention costs (54), although this does not exclude that the COPD subgroup is cost-effective. The Telescot initiative for COPD patients concludes that their telehealth initiative was associated with a non-significant QALY-gain and higher costs (55). A study based in Northern Ireland also concludes that telehealthcare is not cost-effective (56). Our findings are similar (non-significant QALY-gain and higher costs), but contrary to the UK experiences, it is not the intervention costs alone that have a considerable effect on the cost-effectiveness of telehealthcare, but rather differences in community care costs and the failure to save costs on COPD-related hospital contacts.

Implications for clinicians and decision-makers

When interpreting small differences in effectiveness, it is important to be aware that results can be highly sensitive to between-group differences in death. Even though, it is standard practice to assign an EQ5D summary score of 0 to deceased patients (40) in order to calculate incremental QALYs, this practice could potentially have a drastic effect on estimated cost-effectiveness. However, in this case the estimated between-arm QALY difference from the imputed dataset and an analysis where this EQ5D scoring is not done, are similar (QALY difference reduced from 0.01316 to 0.01004).

With regard to cost-differences, it was suspected that baseline differences in costs could occur that would not necessarily be explained by differences in health or sociodemographic characteristics, e.g. due to variations in visitation practice across municipality districts. The results demonstrate a big difference between adjusted and unadjusted costs

and this raises the issue of the relevance of adjusting for baseline cost, if it makes such a large difference in a randomized study design. If baseline cost is removed as a covariate in the analysis of adjusted total costs, incremental costs rise from €728 to €1334. Recent guidance for trial-based cost-effectiveness evaluation suggest that baseline resource use should be collected and that the analysis of both costs and effects *could* include baseline measures of costs (41), which is also recommended by van Asselt et. al.(57). However, guidance is not as explicit as including baseline utility in the analysis of QALYs (58). In our opinion, the baseline difference in cost reported in this study underlines the importance of requesting information on institutional context, such as variations in existing resource patterns, when interpreting cost-effectiveness research.

Danish decision-makers has determined that if the telehealthcare solution in this trial proves cost-effective, it can serve as a national Danish standard for a technological platform as well as an implementation model for telehealthcare to this patient group (59). However, the results suggest that the target COPD-population in this study may have proven to be too broad. An implication could be that decision-makers should await further research, at least into sources of heterogeneity or explanations of the results from this trial. E.g. there was a 10% difference in service cost before inclusion of intervention-related costs and plausible explanations could be that patients randomized to telehealthcare became more aware of their disease and hence used more resources or it could be that especially municipalities discovered patients with an unmet need for e.g. home care when telehealthcare was introduced. Future research planned within this trial would seek to tap into explanations for this difference. It is unknown whether the telehealthcare solution has released its full potential for cost-effectiveness. It is therefore important for healthcare professionals and decision-makers to spend time learning from the experiences gained within the trial in order to investigate if any best practices could be implemented that would increase effectiveness and/or reduce cost without compromising safety and effectiveness.

Future studies

This study indicates that telehealthcare could potentially assist not only in hindering some COPD-related hospital contacts, but also hospital contacts associated with other diseases (incremental costs were reduced by applying all-cause hospital contacts). It could be a coincidence but also due to closer collaboration between healthcare delivery organizations or more frequent monitoring of physical measurements that may also be indicative of other diseases. Future studies should therefore investigate the link between telehealthcare, COPD patients with well-defined comorbidities and hospital contacts.

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Average cost-effectiveness estimates applied in this and other studies could in general hide important sources of heterogeneity. Not much is known on prognostic criteria (e.g. socio-demographic-, geographic-, lifestyle- or health characteristics of the patients) for cost-effectiveness of telehealthcare to chronically ill patients, so further heterogeneity studies should be conducted and are also planned within this trial.

Telehealthcare is a complex intervention involving not only a broad class of technologies, but also organizational infrastructures, actions of healthcare professionals and patients. Experimental evaluation research has been criticized for being a-theoretical in nature in trying to understand why and under what circumstances complex interventions are (un)likely to lead to desired outcomes (60). In this study, mechanisms leading to higher health-related quality of life and cost in the telehealthcare group has largely been treated as a black-box, where patient education, monitoring, emotional support, assisted planning etc. could all have an effect (13). We would recommend, that future cost-effectiveness studies are more informed by a program theory, such as the TECH model (61) that were used in the Healthlines cost-effectiveness studies (62,63). These studies explicitly sought to describe implementation context or account for the causation of the most important telehealthcare-activities that were most likely to activate mechanisms that could lead to “efficient” design and deployment of telehealthcare.

ACKNOWLEDGEMENTS

The authors would like to thank the participants for their time and effort in conduction physical measurements and completing study questionnaires. Also thanks to the North Denmark Region, the 26 municipality districts and around 344 general practitioners in the region for facilitating the implementation the trial.

DECLARATIONS

Detailed description of intervention and comparator: The study protocol includes a detailed description of the intervention and comparator. The study protocol is freely available and can be found at <http://www.trialsjournal.com/content/15/1/178>.

Details of contributors: OH is the principal investigator for the TeleCare North trial and LHE is lead investigator for the economic evaluation in the trial; LHE and OH planned the overall trial design and are guarantors of the statistical quality for the trial as a whole. FWU and PHL contributed to the detailed planning of the data collection of trial questionnaires. FWU planned and collected register data. FWU planned and conducted all analyses under the supervision of LHE and OH. FWU reported the analyses. All authors met regularly during and after the trial period and contributed as a whole to interpreting and the presentation of the data. All authors reviewed and approved the manuscript. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding: This is an independent manuscript commissioned and jointly funded by North Denmark Region, the 26 municipality districts in North Denmark Region, The Obel Family Foundation, the Danish Agency for Digitalization Policy and Strategy, the European Social Fund and Aalborg University.

Competing interests: There are no competing interests. All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author).

Ethical approval: The study is conducted in accordance with the Helsinki Declaration. The trial has been presented to the Regional Ethical Committee for Medical Research in the North Denmark Region where it was determined that no ethical approval was necessary. The trial has also been authorized by the Danish Data Protection Agency. All patients signed an informed consent form before taking part in the clinical trial.

Data sharing: No additional data available

Transparency: OH and LHE affirm that the manuscript is an honest, accurate, and transparent account of the study being reported and no important aspects of the study have been omitted.

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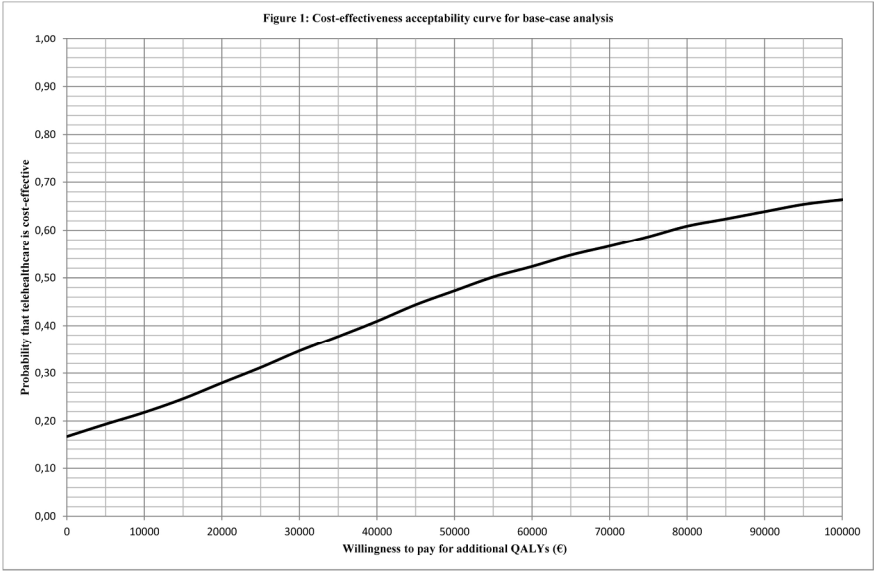
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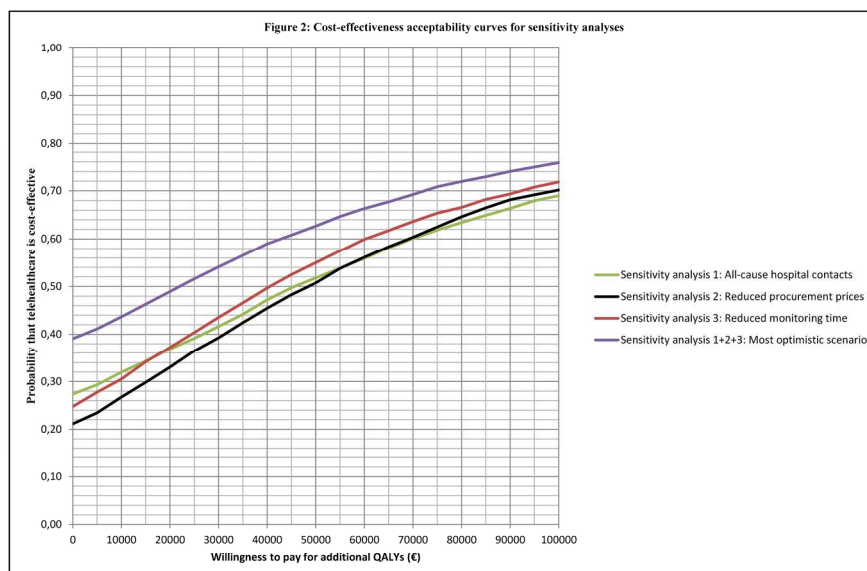
FIGURE LEGENDS

Figure 1: Cost-effectiveness acceptability curve in the base-case analysis

Figure 2: Cost-effectiveness acceptability curves for sensitivity analyses



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Additional file 1

Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Checklist
Items to include when reporting economic evaluations of health interventions

Section/Topic	Item No	Recommendation	Reported on page No / Line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	P1, 1 sentence
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	P2
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Study protocol P4, L1-18
		Present the study question and its relevance for health policy or practice decisions.	Study protocol P4, L19-22
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Study protocol Table 2
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Study protocol Table 1
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Study protocol P2, L12 P5, L3
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Study protocol Table 1
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Study protocol P2, L3 P5, L2
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	P8, L4
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Study protocol P8, L13-19
Measurement of effectiveness	11a	<i>Single study-based estimates:</i> Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Study protocol
	11b	<i>Synthesis-based estimates:</i> Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	N/A

Measurement and valuation of preference-based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	N/A
Estimating resources and costs	13a	<i>Single study-based economic evaluation:</i> Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	P6, L1 to P8, L6
	13b	<i>Model-based economic evaluation:</i> Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	N/A
Currency, price data, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	P8, L7
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	N/A
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	N/A
Analytic methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	P9, L21 to p10, L7
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 2 Table 3 Table 4
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 5
Characterizing uncertainty	20a	<i>Single study-based economic evaluation:</i> Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	Table 5 Figure 1 Figure 2 P15, L1-L13
	20b	<i>Model-based economic evaluation:</i> Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	N/A
Characterizing heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	N/A
Discussion			
Study findings, limitations, generalizability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	P15, L14 to end P16 to p19
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis.	P20

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		Describe other non-monetary sources of support.	
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	P20

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BMJ Open

Cost-effectiveness of telehealthcare to patients with chronic obstructive pulmonary disease: Results from the Danish "TeleCare North" cluster-randomized trial.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-014616.R2
Article Type:	Research
Date Submitted by the Author:	24-Mar-2017
Complete List of Authors:	Witt Udsen, Flemming; Aalborg University, Danish Centre for Healthcare Improvements Lilholt, Pernille; Aalborg University, Department of Health Science and Technology Hejlesen, Ole; Aalborg University, Department of Health Science and Technology Ehlers, Lars; Aalborg University, Danish Centre for Healthcare Improvements
Primary Subject Heading:	Health economics
Secondary Subject Heading:	Health policy, Medical management, Patient-centred medicine
Keywords:	BIOTECHNOLOGY & BIOINFORMATICS, Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS, HEALTH ECONOMICS

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Cost-effectiveness of telehealthcare to patients with chronic obstructive pulmonary disease: Results from the Danish “TeleCare North” cluster-randomized trial

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ABSTRACT

Objectives: To investigate the cost-effectiveness of a telehealthcare solution in addition to usual care compared with usual care.

Design: A 12 month cost-utility analysis conducted alongside a cluster-randomized trial.

Setting: Community based setting in the geographical area of North Denmark Region in Denmark.

Participants: 26 municipality districts define randomization clusters with 13 districts in each arm. 1,225 patients with chronic obstructive pulmonary disease were enrolled of which 578 patients were randomized to telehealthcare and 647 to usual care.

Interventions: In addition to usual care, patients in the intervention group received a set of telehealthcare equipment and were monitored by a municipality-based healthcare team. Patients in the control group received usual care.

Main outcome measure: Incremental costs per quality-adjusted life-years gained from baseline up to 12 months follow-up.

Results: From a healthcare and social sector perspective, the adjusted mean difference in total costs between telehealthcare and usual care was €728 (95% CI: -754; 2211) and the adjusted mean difference in quality-adjusted life-years gained was 0.0132 (95% CI: -0.0083; 0.0346). The incremental cost-effectiveness ratio was €55,327 per quality-adjusted life-year gained. Decision-makers should be willing to pay more than €55,000 to achieve a probability of cost-effectiveness greater than 50%. This conclusion is robust to changes in the definition of hospital contacts and reduced intervention costs. Only in the most optimistic scenario combining the effects of all sensitivity analyses, does the incremental cost-effectiveness ratio fall below UK thresholds values (€21,068 per quality-adjusted life-year).

Conclusions: Telehealthcare is unlikely to be a cost-effective addition to usual care if it is offered to all patients with chronic obstructive pulmonary disease and if the willingness-to-pay threshold values from National Institute for Health and Care Excellence are applied.

Trial registration: Clinicaltrials.gov, NCT01984840, November 14, 2013.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study reports the within-trial cost-effectiveness of a pragmatic large-scale asynchronous telehealthcare initiative in order to improve the international evidence base of the economic effects of telehealthcare for COPD patients.
- A relatively broad health care and social sector perspective was chosen and the cost-analyses of resource use are based on register data.
- A limitation of the study is that only 61% of the participants had complete registrations of all cost-categories and outcomes.
- The way telehealthcare was implemented may have affected cost-effectiveness, since the involved organizations and healthcare professionals underwent a steep learning curve after implementation of the telehealthcare solution, where they had to find new ways of working together and adapt to new work procedures.

Keywords: RCT; Telehealth; Telecare; Telemonitoring; COPD; Economic Evaluation; Cost-effectiveness; Denmark

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease (1). The main symptoms of COPD are dyspnea, recurrent lung infections, abnormal sputum, wheezing, decreased exercise tolerance and “smoker’s cough” (2). Depending on the severity of COPD, patients can experience a number of exacerbations, where symptoms become more severe than normal, which are often associated with a further progression of the disease (2) and anxiety (3). COPD is one of the most prevalent and deadly diseases in the world (4). The global prevalence of COPD is high (11,7%) (5). COPD is associated with high mortality (6), presence of comorbidities (7,8) and reduced health-related quality-of-life (9,10). COPD poses a substantial financial burden on healthcare systems, e.g. the annual direct costs for COPD has been estimated to \$20-26 billion in the US with hospital admissions representing 52-70% of all direct costs (11). A recent Danish study has estimated that COPD is responsible for 8,300 years of life lost and €174 million in annual direct cost for treatment and care (12).

Telehealthcare has been suggested as a possible effective intervention to patients with COPD on especially health-related quality-of-life (13). Telehealthcare is a technology that contains data from a patient which is transferred electronically over a physical distance and healthcare professionals exercise their judgment in providing personalized feedback to the patient based on these data (14). Some feasibility studies including cost-analyses have previously suggested an added value of telehealthcare compared to usual practice and some of these studies show that telehealthcare may lower hospital or healthcare costs (15–19). But most recent systematic reviews have questioned the quality of this evidence and have requested more cost-effectiveness evaluations (20–24), preferably with broader cost-perspectives (25).

The objective of this paper is to add to this international evidence base on the cost-effectiveness of telehealthcare by presenting the results of a cost-utility analysis of a telehealthcare intervention to patients with COPD compared with usual practice. The analysis was nested within a 12-months cluster-randomized trial (called “TeleCare North”) that were conducted in the geographic area of North Denmark Region in Denmark from 2013-2014.

METHODS

A more detailed trial protocol has been published elsewhere (26), but a brief summary is provided in Table 1. 26 municipality districts in North Denmark Region define the randomization clusters with 13 districts in each arm. In addition to usual care, patients in the intervention group received a set of telehealthcare equipment and were monitored by a community-based healthcare team. Patients in the control received usual care.

Table 1: Description of the Danish TeleCare North cluster-randomized trial	
Eligible criteria for clusters	All municipalities in North Denmark Region except one (a small island off the coast), 10 municipalities in all. Each municipality consisted of between 2 and 5 municipality districts and these districts were randomization units, 26 municipality districts in total (13 in each arm).
Eligible criteria for patients	COPD as primary disease, diagnosis by spirometry, in treatment according to guidelines recommended by “The Global Initiative for Chronic Obstructive Lung Disease (GOLD)” (1), at least two exacerbations within the past 12 months, motivated for treatment, fixed residence in North Denmark Region, The Modified Medical Research Council scale (mMRC) ≥ 2 or mMRC ≥ 3 and COPD Assessment Test (CAT) ≥ 10 . Exclusion criteria were: no phone line or Global System for Mobile communications (GSM) coverage, unable to understand Danish sufficiently to complete the study questionnaires or diagnosed with a cognitive impairment.
Intervention group: Cluster-level intervention	Municipality district healthcare personnel (primarily nurses and health assistants) were trained in two separate sessions. One session focused on the technical aspects of the tablet and physical measurements. Another session focuses on general disease awareness and communication with patients. The training was performed by members of the trial administration office. General practitioners were responsible for establishing threshold values for physical measurements. Nurses in the patient’s residing municipality were responsible for monitoring the data obtained and should incorporate monitoring time duties with their existing job responsibilities. Exemptions were COPD patients receiving oxygen therapy and COPD patients with open hospital admissions who were monitored at their hospital as usual. Patients were monitored asynchronously by a nurse on a daily basis. Measurements were classified with either a green, yellow or red code (Green code: no threshold values were exceeded. Yellow code: one or more values exceeded the threshold values. Red code: one or more values exceeded the threshold values and had not previously been recorded). The nurse had the option to contact the patient by telephone and/or the patient’s general practitioner and/or dispatch an ambulance. Installation, swopping of defects, de-installation and technical support and maintenance of the equipment was handled by IT-specialists.
Intervention group: Patient-level intervention	Telephone contact to each patient from municipality healthcare personnel no later than 10 days after randomization, and a 45-minute appointment scheduled for patients who wanted to receive the tablet at home. For those who wished to receive the tablet at a municipality health center, a 75-minute appointment was scheduled with 3 to 4 patients in each group. At both appointments, a nurse from the patients’ municipalities demonstrated the use of the tablet and instructed patients in how to conduct physical measurement. Patients were asked to measure their vital signs daily during the first two weeks (both weekdays and weekends) and 1 to 2 times weekly after the two first weeks. A 45-minute follow-up visit was scheduled 3 to 4 weeks after the first appointment to check if the patient used the device appropriately and if the threshold values of the physical measurements needed to be adjusted.
Intervention group: Device	All patients received the same device and peripherals. It consisted of a standard tablet (Samsung Galaxy) containing information on handling COPD in general and software (two apps) that automatically instructs the patient in handling COPD during exacerbations. The tablet can collect and wirelessly transmit data on blood pressure, pulse, blood oxygen saturation, and weight via an attached Fingertip Pulse Oximeter, a Digital Blood Pressure Monitor, and a scale.
Control group: Usual Care	Usual practice for caring for patients with COPD is the responsibility of the patient’s general practitioner (treatment and monitoring) and the municipalities (practical help and home nursing care). COPD patients can make appointments with their general practitioner or call the emergency contact number without copayment in order to get treatment or advice in managing COPD but this advice is not personalized. Community care administered by municipality district personnel comes at regular intervals based on a clinically based estimate of the patients’ needs, but these personnel are not necessarily certified nurses and often not fully educated in COPD and not on call.

The primary outcome measure for the cost-effectiveness analysis was the incremental cost-effectiveness ratio (ICER) expressed as the total cost per quality-adjusted life-year (QALY) gained measured from baseline to follow-up at 12 months. In defining the total costs, this trial adopted a healthcare and social care sector perspective (including hospital services, primary care, medicine, home care services and rehabilitation).

Healthcare service use and healthcare costs

Healthcare and social care service use were all estimated based on register data by applying a unique civil registration number that all Danish citizens have and that makes precise linkage between registers possible. National patient-level data for all hospital contacts were collected from the Danish National Patient Register (27), which contains all inpatient, outpatient and emergency ward visits in Denmark. The total costs for each contact is a variable in these datasets and are valued based on the diagnose-related group (DRG), the actual procedures conducted and the duration of the contact (28). The included admissions, outpatient and emergency ward visits were in the main analysis restricted to those defined as COPD-specific in the Danish Register for COPD (29).

All contacts between patients and the primary care sector were collected from the National Health Insurance Service Register (30). The costs for each contact is part of the dataset and are valued based on fees negotiated in a collective agreement (31). At present, it is not possible to identify the cause of contact to the primary care sector, so all contacts are included.

Medication use was taken from The Danish Register of Medicinal Product Statistics that contains information about what prescribed medicine citizens purchase in Denmark (32). For this analysis these are restricted to patient-level medicine associated with COPD (R03 ATC codes), specific antibiotics, antifungals and medicine for anxiety, all associated with the treatment of COPD-exacerbations, as well as medicine for smoking cessation. The costs for each product is given in this dataset and is valued based on a standardized pharmacy consumer price (33).

Patient-level community care service use was collected from individual care systems in each of the 26 included municipality districts. The type and duration of standard care activities such as personal care, practical help, home nursing care and rehabilitation activities are routinely recorded for each contact. Each municipality district values contacts differently based on an internal calculated mean hourly cost. It was pragmatically decided to value time consumption in municipality districts as an average of the reported hourly costs from municipality districts. Four of the 26 municipality districts in the trial were implementing a different IT-system at the time of data collection which meant that rehabilitation costs for these four municipality districts were unavailable (2 municipality districts in the telehealthcare group and 2 in the usual care group).

Healthcare service use was collected for 12-months to allow for within-trial costs to be calculated. In addition, patient-level health service use was also collected 12 months prior to randomization, because it was suspected that baseline

differences in costs could occur that would not be explained by differences in health status or socio-demographic characteristics by patients, e.g. due to variations in referral and visitation practices across municipality districts.

Intervention costs

Costs associated only with the clinical trial, preparing the organization and developing the telehealthcare solution were excluded. Intervention costs were costs of hardware and peripherals, installation and deinstallation costs, maintenance and support costs, training costs for healthcare professionals, patient specific training, monitoring costs and project management costs.

Per person costs of the “package” of telehealthcare equipment (the so-called “Telekits” consisting of a tablet and peripherals) were calculated. The “Telekits” supplied were exactly the same for all patients and was purchased to each patient ahead of the trial and valued as prices paid. The per person costs of installation/deinstallation and swapping any defects in the equipment was negotiated with an external supplier prior to the trial and valued as prices paid. Per patient maintenance and support costs consisted of software licenses and data charges, technical support to patients and healthcare professionals as well as IT-infrastructure- and application maintenance and valued as prices paid. Costs associated with IT-infrastructure- and application maintenance was not dependent on the number of patients in the trial but the software and hardware configuration employed by the telehealthcare solution which in principle could include all COPD patients and patients with chronic heart failure. It was decided to allocate these costs on the estimated number of COPD and chronic heart failure patients in North Denmark Region (10,500 patients) (34,35). The per patient costs of training healthcare professionals were based on planned time spent conducting education workshops in COPD disease awareness and the telehealthcare solution, the number of conducted workshops and the average hourly wage for a community district nurse. Per patient costs of patient specific training were based on planned time and valued based on a mean hourly wage for a community district nurse. Time spent per patient on monitoring were estimated by time registries in the municipality districts and valued based on a mean hourly wage for a community district nurse. Based on the experiences gained with the implementation in the trial period, it was estimated that it would be necessary to have an administrative officer employed to “run” the telehealthcare solution, should it be implemented in routine practice (coordinating activities, contract supervision etc.). Project management costs were valued as mean yearly salary for an administrative officer including all standardly available pensions and pay supplements (36). As with IT-infrastructure- and application maintenance, these costs could be allocated on more patients than in the trial and they were therefore

also allocated on the estimated number of COPD and chronic heart failure patients in North Denmark Region (10,500 patients) (34,35).

Equipment costs (the Telekits), installation/deinstallation costs, costs associated with training healthcare professionals and patient specific training were annuitized over a period of five years with a discount rate of 3% p.a. and presented as equivalent annual cost. 5 years and 3% can be used as standard lifetime and discount rate for “other IT-equipment” in Danish capital accounting (37).

All costs are reported in 2014 prices. Costs were obtained in Danish kroner (DKK) and exchanged to Euro (€) using the average 2014 exchange rate (1€ = 7.4547DKK). All healthcare service use and costs are reported as means and standard errors and where descriptive statistics are presented, differences between intervention and control group means are reported as raw differences and, to allow for future meta-analysis, as standardized differences (the raw difference between group means, divided by the standard deviation of the total sample) presented as a percentage.

Effectiveness

Information of mortalities were obtained from the Danish Register of Causes of Death (38) which contain mortality statistics on all deaths in Denmark. Utility scores stem from the EQ5D-3L health-related quality-of-life questionnaire with Danish societal weights (39). QALYs were calculated by linear interpolation of utility scores. The health-related quality-of-life items and relevant demographic data were collected at baseline by help from the patients’ general practitioners who distributed the questionnaires to all patients but with a prepaid return envelope to the trial administration office. At follow-up, a questionnaire consisting of the health-related quality-of-life items were sent from the trial administration office to the patients’ home addresses with a prepaid return envelope.

ANALYSIS

Statistical analyses were all performed in STATA version 12.1 except the probabilistic sensitivity analysis that was developed in Microsoft Excel 2010.

Missing data

1,225 patients were randomized in the study (578 patients in the telehealthcare group and 647 in the control group). At baseline, missing data for the EQ5D summary score were present for 8% of the participants (48 in the telehealthcare group; 53 in the control group). 103 patients died during the trial period (8%; 50 in telehealthcare group; 53 in control group) and they were assigned an EQ5D summary-score of 0 at follow-up that were used in the QALY calculation (40). In addition, 27% had missing data on the EQ5D summary score at follow-up (199 in the telehealthcare group; 133 in the

control group) either due to non-response or to incomplete registration of EQ5D questionnaire items. 12% had missing values on rehabilitation costs (79 in the telehealthcare group; 73 in the control group). Complete data for both total costs (i.e. all cost-categories), baseline EQ5D-score and EQ5D-score at follow-up were available for 751 patients (61%; 325 in telehealthcare group; 426 in control group).

Current good practice for trial-based economic evaluation recommends that analyses should account for missing data by imputation, especially when there is a large amount of missing data (41). The applied imputation procedure followed the principles recommended by Faria and colleagues (42). Missing data were assumed missing at random (MAR), which can be a plausible assumption if a wide range of variables, and variables that are predictive of missingness, are included in the imputation model (43). Therefore, missing data on EQ5D scores, rehabilitation costs and baseline characteristics were imputed using the *mi impute chained* command in STATA12.1 and 30 complete datasets were created. Continuous variables were imputed by predictive mean matching and categorical variables by multinomial logistic or logistic regression. Imputation models included outcome variables, predictors for the outcomes at both time points and predictors for missing observations in the individual variables. The imputation models were estimated separately by treatment group and included the clustering variable, measures of health-related quality-of-life (EQ5D scores), costs at baseline or at 12 months follow-up (in the categories presented in Table 4), measures of disease status (forced expiratory volume in one second (FEV1%), forced vital capacity (FVC%), diastolic- and systolic blood pressure), smoking status, presence of comorbidities (diabetes, cancer, cardiovascular disease, mental illness or musculoskeletal disorders) and socio-demographic variables (age, gender, marital status, education and employment status).

Cost-effectiveness analysis

The cost-effectiveness analysis followed an intention-to-treat principle. The statistical analysis applied multilevel modeling for continuous variables that rely on near-normality (44), which has been suggested as an analysis strategy for cost-effectiveness research of cluster-randomized trials (45). To allow for different sets of covariates, estimation of incremental total costs and incremental QALYs gained was based on two separate linear mixed effects models; one for total costs and one for QALYs. Total costs were controlled for treatment arm, baseline EQ5D score, baseline costs (total costs 12 months prior to randomization), age, baseline FEV1%, presence of musculoskeletal disease (a significant cost driver in municipality districts) and clustering. QALYs gained were controlled for treatment group, baseline EQ5D score, age, gender, baseline FEV1%, marital status, presence of diabetes, presence of cancer and clustering. These

estimations were facilitated by the *mi estimate: xtmixed* command with robust standard errors. A deterministic ICER-estimate was calculated using the treatment beta-coefficients from these two models. In order to explore the uncertainty surrounding cost-effectiveness, the output from the *mi estimate: xtmixed* was exported to Microsoft Excel 2010 along with Cholesky's decomposition matrix to allow for a potential correlation between all the parameters in the analyses models. By redrawing new parameter estimates from the estimated treatment-effect with its standard error, 5,000 simulations were calculated to obtain new estimates of incremental QALYs and incremental total costs which were used to construct cost-effectiveness acceptability curves.

Sensitivity analysis 1: All-cause hospital contacts

In the base-case analysis, we have sought to limit hospital contacts to COPD-specific contacts because the hypothesis were that telehealthcare could prevent a proportion of admissions and emergency ward visits associated with exacerbations and make most COPD-specific outpatient control visits redundant. However, it became apparent that the included patients suffer from a variety of diseases concomitant with COPD (see Table 2). As part of the intervention, it is therefore plausible that a more integrated care and monitoring approach assisted by the telehealthcare technology could also prevent some hospital contacts due to comorbidities. Some of the measurements facilitated by the Telekits could e.g. be indicative of cardiovascular disease and especially chronic heart failure. The effect on incremental costs of including all hospital contacts was therefore explored.

Sensitivity analysis 2: Reduced procurement prices and larger scale

Potential discounts on procurement prices could be achieved when contemplating to implement technologies on a larger scale and increased capacity of the telehealthcare solution could also drastically reduce intervention cost thereby affecting the cost-effectiveness conclusion. Therefore, an effect of a 30% discount on Telekit equipment, installation, support and maintenance was explored. 30% is an estimate stemming from experiences with negotiating procurement prices subject to large-scale implementation of telehealthcare in the Danish healthcare sector (46). In addition, suppliers have stated that the costs of maintenance (IT-infrastructure and applications) and support costs does not depend on the number of patients included, but the complexity of the hardware and software configuration. The effects of making these costs negligible due to very large-scale implementation were therefore also explored.

Sensitivity analysis 3: Reduced monitoring time

Municipality healthcare personnel had a steep learning curve for their new monitoring tasks and the patients' need for monitoring was uncertain at the outset. This resulted in approximately 5 minutes of average monitoring time per patient

per week in the trial. After 12 months, personnel had become more efficient at monitoring and responding to vital values, so a new average target of 2 minutes per week per patient (i.e. 110 minutes annually) have been discussed by the North Denmark Region and the municipality districts (47) and the effects of this target on cost-effectiveness is investigated.

Finally, a most optimistic scenario exploring the combined effect of sensitivity analyses 1, 2 and 3 was investigated. The effect on total costs and/or QALYs was explored using the same models and covariates as the base-case analysis.

RESULTS

Baseline characteristics of all the included patients are presented in Table 2. Baseline characteristics are fairly balanced across treatment groups. The FVC(%) is lower in the telehealthcare group and there is an overall tendency for patients in the telehealthcare group to have slightly worse health (lower average lung function, lower average health-related quality of life, higher average proportion of comorbidities (except musculoskeletal disorders)). The number of smokers is higher in the intervention arm and baseline costs were also higher in the telehealthcare group.

Table 2: Baseline characteristics			
	All 1,225 participants at baseline		
	Telehealthcare	Usual care	Difference
	n=578	n=647	Raw
Age (years)§	69.55 (9.36)	70.33 (9.11)	-0.78
Men (%)§	48.27 (n=279)	43.74 (n=283)	4.53
Marital status (%)			
Married/In a relationship	55.88 (n=323)	54.25 (n=351)	1.63
Single	20.42 (n=118)	22.10 (n=143)	-1.68
Widow/Widower	16.78 (n=97)	16.54 (n=107)	0.24
Missing (%)	6.92 (n=40)	7.11 (n=46)	-0.19
Smoking status (%)			
Non-smokers	59.34 (n=343)	63.06 (n=408)	-3.72
Smokers	33.91 (n=196)	29.21 (n=189)	4.70
Missing (%)	6.75 (n=39)	7.73 (n=50)	-0.98
Duration of COPD (years)	7.80 (6.23)	7.70 (5.79)	0.10
Missing (%)	14.01 (n=81)	15.14 (n=98)	-1.13
FEV1(%)	47.70 (18.05)	48.37 (18.94)	-0.67
Missing (%)	18.51 (n=107)	19.78 (n=128)	-1.27
FVC(%)	70.38 (20.02)	74.34 (22.33)	-3.96
Missing (%)	34.43 (n=199)	39.41 (n=255)	-4.98
Comorbidities (%)			
Diabetes	10.21 (n=59)	9.89 (n=64)	0.32
Coronary heart disease	32.70 (n=189)	31.84 (n=206)	0.86

Mental health problem	4.84 (n=28)	4.79 (n=31)	0.05
Musculoskeletal disorder	24.91 (n=144)	29.37 (n=190)	-4.46
Cancer	6.06 (n=35)	4.79 (n=31)	1.27
Missing (%)	8.13 (n=47)	7.88 (n=51)	0.25
Baseline total costs (€)\$	6492 (14150)	4900 (7149)	1592
Missing (%)	13.66 (n=79)	11.28 (n=73)	2.38
Baseline EQ5D	0.706 (0.202)	0.716 (0.185)	-0.010
Missing (%)	8.30 (n=48)	8.19 (n=53)	0.11

Data are mean (standard deviation) or proportion (number of patients)

COPD: chronic obstructive pulmonary disease; FEV1(%): forced expiratory volume in one second of predicted normal;

FVC(%): forced vital capacity

\$Variable has no missing values

\$Baseline total costs are missing for 3 cost categories (Help and care at home, Community or district nurse and Rehabilitation, see Table 4) in 4 municipality districts

The unadjusted healthcare service use over the trial period with unit costs sources is summarized in Table 3. Average values for healthcare service use were not imputed (i.e. values are based on non-missing cases unadjusted for patient case mix). Table 3 reveals that resource use is consistently higher in the telehealthcare group.

Table 3: Service use at 12 months across treatment groups and applied unit costs

	Mean (SE) contacts		Between group difference		Unit	Unit cost
Service use	Telehealthcare (n=578)	Usual care (n=647)	Raw	Standardized (%)*		
<i>Hospital contacts</i>						
Admissions	0.5 (0.05)	0.45 (0.49)	0.046	3.70	Per contact	DRG value of contact (28)
Inpatient bed days	2.69 (0.31)	2.60 (0.31)	0.09	1.18	Per contact	Included in DRG value of contact (28)
Outpatient/emergency department visits	0.87 (0.08)	0.74 (0.07)	0.13	7.16	Per contact	DRG value of contact (28)
<i>Primary care contacts</i>						
General practitioner	10.72 (0.35)	9.92 (0.33)	0.80	9.35	Per contact	Tariffs from Collective agreement (31)
<i>Municipality care (time spent)</i>						
Help and care at home	2137.32 (275.17)	1614.09 (207.76)	523.24	8.79	Per hour	Average hourly cost across municipalities (€57)
Community or district nurse	607.29 (100.95)	438.59 (73.00)	168.69	7.86	Per hour	Average hourly cost across municipalities (€75)
Rehabilitation§	77.75 (14.34)	53.00 (13.21)	24.75	7.77	Per hour	Average hourly cost across municipalities (€75)

<i>Medicines</i>						
No of Antibiotics	2.41 (0.13)	1.89 (0.11)	0.52	17.28	Various	Pharmacy consumer price (33)
No of R03 ATC codes (COPD medicine)	25.08 (0.68)	23.92 (0.65)	1.16	7.08	Various	Pharmacy consumer price (33)

*Standardized difference: difference between randomization group averages divided by the standard deviation of the total sample
§Incomplete register-data. Data unavailable for 4 municipality districts (2 in the control group and 2 in the intervention group, respectively)
SE = Standard error of the mean

The unadjusted within-trial costs are summarized in Table 4. The annual per patient healthcare service costs (excluding intervention costs) were higher in the telehealthcare group (by €836) driven primarily by higher costs in the municipality districts on practical help and home care as well as costs to community or district nurses. Table 4 also reveals that COPD-specific hospital admissions costs are roughly the same in the telehealthcare and usual care group. Excluding intervention costs, the three largest healthcare service cost drivers in telehealthcare were COPD-specific hospital admissions (34%), costs associated with practical help and care in municipality districts (24%) and medicine (20%). By adding intervention costs (also elaborated in Table 4), the raw mean difference in annual per patient total costs between telehealthcare and usual care was €1540.

Table 4: Average costs per patient across treatment groups at 12 months follow-up (€)				
Service use	Mean (SE) costs		Between group difference	
	Telehealthcare (n=578)	Usual care (n=647)	Raw (€)	Standardized (%)*
<i>Hospital contacts</i>				
Admissions	2756.1 (463.8)	2753.1 (458.9)	3.0	0.02
Outpatient/emergency department visits	343.4 (24.8)	278.3 (21.5)	65.1	11.37
<i>Primary care contacts</i>	602.9 (17.8)	629.4 (20.3)	-26.5	-5.55
<i>Municipality care contacts</i>				
Help and care at home	1936.7 (249.3)	1462.6 (188.2)	474.1	8.79
Community or district nurse	733.4 (121.9)	529.7 (88.1)	203.7	7.86
Rehabilitation§	93.4 (11.01)	61.0 (10.57)	32.4	8.56
<i>Medicine</i>	1610.1 (45.2)	1525.7 (37.7)	84.4	8.26
<i>Service costs (excluding intervention costs)</i>	8076.0 (417.6)	7239.8 (411.5)	836.2	5.76
Project Management	7.4	0	7.4	-
Computer hardware and peripherals	200.5	0	200.5	-
Installation	38.6	0	38.6	-
Maintenance and Support	94.6	0	94.6	-
Training healthcare professionals	12.4	0	12.4	-

Patient specific training	20.6	0	20.6	-
Monitoring vital signs	330.0 (12.76)	0	330.0	123.43
<i>Total costs (including intervention costs)</i>	<i>8780.2 (417.2)</i>	<i>7239.8 (411.5)</i>	<i>1540.4</i>	<i>10.61</i>

*Standardized difference: difference between randomization group averages divided by the standard deviation of the total sample

§Imputed data

SE = Standard error of the mean

Table 5 presents the results of the incremental analyses. The base-case unadjusted average difference in QALYs was 0.0062 (not statistically significant) and the unadjusted difference in total costs was €1219 per patient. The base-case adjusted average difference in QALYs was 0.0132 (not statistically significant) with an adjusted average difference in annual total costs of €728 per patient. Based on these estimates, the ICER is €55,327 per QALY. This telehealthcare solution is therefore only cost-effective if the willingness-to-pay threshold exceeds the ICER estimate.. Figure 1 presents the cost-effectiveness acceptability curve (CEAC) and it can be seen that decision-makers should be willing to pay more than €55,000 to achieve a probability of cost-effectiveness greater than 50%.

Table 5: Incremental costs (€) and incremental QALYs at 12 months follow-up		
n=1,225 (Telehealthcare: n=578; Usual care n=647)	Between group difference (95% CI) or ICER	Intra-class coefficient (ICC)
Base-case analysis		
QALY (unadjusted mean difference)*	0.0062 (-0.0307; 0.0431)	0.007
Costs (unadjusted mean difference)*	1219 (-937; 3376)	0.014
QALY (adjusted mean difference)**	0.0132 (-0.0083; 0.0346)	0.000
Costs (€) (adjusted mean difference)***	728 (-754; 2211)	0.014
ICER (adjusted, € per QALY)	55,327	
Sensitivity analysis 1: All-cause hospital contacts		
Costs (€) (adjusted mean difference)***	583 (-1397; 2563)	0.005
ICER (adjusted, € per QALY)	44,301	
Sensitivity analysis 2: Reduced procurement prices and larger scale		
Costs (€) (adjusted mean difference)***	618 (-865; 2100)	0.014
ICER (adjusted, € per QALY)	46,931	
Sensitivity analysis 3: Reduced monitoring time		
Costs (€) (adjusted mean difference)***	525 (-969; 2018)	0.012
ICER (adjusted, € per QALY)	39,854	
Sensitivity analysis 1+2+3: Most optimistic scenario		
Costs (€) (adjusted mean difference)***	277 (-1700; 2255)	0.014
ICER (adjusted, € per QALY)	21,068	

QALY: Quality adjusted life years

ICER: Incremental cost-effectiveness ratio

* Linear mixed model with treatment arm as only covariate
** Linear mixed model adjusted for treatment arm, baseline EQ5D score, age, gender, baseline FEV1%, marital status, presence of diabetes, presence of cancer and clustering
*** Linear mixed model adjusted for treatment arm, baseline EQ5D score, baseline costs, age, baseline FEV1%, presence of musculoskeletal and clustering.

Sensitivity analyses

Results from sensitivity analyses are also presented in Table 5 and CEACs for all scenarios are presented in Figure 2. In sensitivity analysis 1, all-cause hospital contacts were included in the analysis. Incremental total costs remain higher in the telehealthcare groups (€583) with an ICER of €44,301 per QALY. From Figure 2, it can be seen that the willingness-to-pay threshold falls to €45,000 per QALY to achieve a probability of cost-effectiveness greater than 50%. By reducing procurement prices and operating on a larger scale (sensitivity analysis 2), incremental total costs falls to €618 (ICER=€46,931 per QALY). The willingness-to-pay threshold is €49,000 per QALY if a probability of cost-effectiveness greater than 50% should be achieved. Sensitivity analysis 3 (reducing average per patient monitoring time from 5 to 2 minutes) would reduce incremental total costs to €525 and the ICER to €39,854. The willingness-to-pay threshold falls to €40,000 per QALY if a probability of cost-effectiveness greater than 50% should be achieved. In the most optimistic scenario combining the results from all sensitivity analyses (1+2+3), the adjusted incremental costs of telehealthcare were €277 giving rise to an ICER of €21,068 per QALY and a willingness-to-pay threshold of €21,000 per QALY to achieve a probability of cost-effectiveness greater than 50%.

DISCUSSION

The adjusted mean difference in QALYs was 0.0132 (-0.0083; 0.0346) and the adjusted mean difference in costs were €728 (-754; 2211) leading to an ICER of €55,327 per QALY. This ICER is higher than any explicit threshold values employed by countries today, e.g. those recommended in the UK (48). The cost-effectiveness conclusion is robust to changes in the definition of hospital contacts and reduced intervention costs. Only in the most optimistic scenario combining the effects of all sensitivity analyses, does the ICER fall below UK thresholds. The telehealthcare solution is therefore unlikely to be cost-effective for all included COPD patients.

Strengths and limitations

This study is the largest trial-based cost-utility study of telehealthcare to COPD patients in Denmark so far. A relatively broad range of cost categories from contacts in healthcare and social services are included and these contacts are all based on register data routinely registered in Denmark. A healthcare and social sector perspective was chosen which excludes transportation costs, time spent by patients and relatives and productivity loss to society. But travel distances in Denmark are relatively short compared to other larger countries (the longest distance to a university hospital is 160 km) and only 11% of the patients enrolled in the trial stated that they are employed (5% are full-time; 6% part-time).

Data on each monitoring contact was available for 21 of the 26 municipality districts included (the remaining 5 districts has reported aggregated time spent monitoring each participant during the trial-period). The median number of monitoring encounters within these 21 districts was 53 out of 64 planned contacts (26). Although monitoring does not represent all facets of adherence and we do not have complete data for each individual encounter, it does suggest that participants in general were willing to engage with the TeleCare North initiative.

A limitation of the study is that single-level multiple imputation with clustering as a fixed effect was performed. Gomes et. al. has found that an imputation approach that account for clustering as a random effect perform better than single-level imputation (49). More specifically, Andridge have in a simulation study found that including clustering as a fixed effect in the imputation model could overestimate the uncertainty of the estimates, especially if the number of clusters are small and the ICC is low as in this case (50). However, a barrier to the adoption of multi-level multiple imputation is that these techniques are not part of conventional statistical software. Furthermore, separate modeling of costs and effects were performed in the analyses of incremental QALYs and costs, which could be less statistically efficient than joint modeling (51), although a multiway sensitivity analysis in a simulated cost-effectiveness study of bivariate multilevel models set to small correlations between costs and outcomes also perform reasonably well under the circumstances of this trial (e.g. a small number of clusters and unequal cluster sizes) (52).

Smoking status is an important risk factor for COPD (53) and the proportion of non-smokers was lower in the intervention arm, which was not accounted for in the randomization (e.g. through minimization). However, the difference in smoking status between intervention and control group is not statistically significant (Fisher's exact test, p-value=0.103) and including smoking status as an additional covariate in the QALY and cost models have little impact on treatment effects (i.e. incremental QALYs is reduced from 0.01316 to 0.01288 with smoking status included and incremental costs is changed from €728 to €705).

The way telehealthcare was implemented may have affected cost-effectiveness. The involved organizations and healthcare professionals underwent a steep learning curve after implementation of the telehealthcare solution, where they had to find new ways of working together and adapt to new work procedures. Monitoring is one example and personnel became more efficient at the end of the trial, when the needs and reactions of patients as well as work tasks were more familiar to municipality healthcare personnel. Other implementation effects such as how care-coordination across municipality districts, hospitals and GPs actually occurred or the engagement of health professionals and involved organizations could also have affected cost-effectiveness, but is hard to quantify post hoc.

Comparison with other studies

To our knowledge, three other studies have recently published cost-effectiveness results for telehealthcare involving COPD patients and they all demonstrated a low probability of cost-effectiveness by the standards of their countries (54–56). A British study (Whole System Demonstrator) concludes that telehealth as a supplement to usual care is not likely to be cost-effective for patients with COPD, diabetes and chronic heart failure primarily due to a “similar” QALY-gain and high intervention costs (54), although this does not exclude that the COPD subgroup is cost-effective. The Telescot initiative for COPD patients concludes that their telehealth initiative was associated with a non-significant QALY-gain and higher costs (55). A study based in Northern Ireland also concludes that telehealthcare is not cost-effective (56). Our findings are similar (non-significant QALY-gain and higher costs), but contrary to the UK experiences, it is not the intervention costs alone that have a considerable effect on the cost-effectiveness of telehealthcare, but rather differences in community care costs and the failure to save costs on COPD-related hospital contacts.

Implications for clinicians and decision-makers

When interpreting small differences in effectiveness, it is important to be aware that results can be highly sensitive to between-group differences in death. Even though, it is standard practice to assign an EQ5D summary score of 0 to deceased patients (40) in order to calculate incremental QALYs, this practice could potentially have a drastic effect on estimated cost-effectiveness. However, in this case the estimated between-arm QALY difference from the imputed dataset and an analysis where this EQ5D scoring is not done, are similar (QALY difference reduced from 0.01316 to 0.01004).

With regard to cost-differences, it was suspected that baseline differences in costs could occur that would not necessarily be explained by differences in health or sociodemographic characteristics, e.g. due to variations in visitation practice across municipality districts. The results demonstrate a big difference between adjusted and unadjusted costs

and this raises the issue of the relevance of adjusting for baseline cost, if it makes such a large difference in a randomized study design. If baseline cost is removed as a covariate in the analysis of adjusted total costs, incremental costs rise from €728 to €1334. Recent guidance for trial-based cost-effectiveness evaluation suggest that baseline resource use should be collected and that the analysis of both costs and effects *could* include baseline measures of costs (41), which is also recommended by van Asselt et. al.(57). However, guidance is not as explicit as including baseline utility in the analysis of QALYs (58). In our opinion, the baseline difference in cost reported in this study underlines the importance of requesting information on institutional context, such as variations in existing resource patterns, when interpreting cost-effectiveness research.

Danish decision-makers has determined that if the telehealthcare solution in this trial proves cost-effective, it can serve as a national Danish standard for a technological platform as well as an implementation model for telehealthcare to this patient group (59). However, the results suggest that the target COPD-population in this study may have proven to be too broad. An implication could be that decision-makers should await further research, at least into sources of heterogeneity or explanations of the results from this trial. E.g. there was a 10% difference in service cost before inclusion of intervention-related costs and plausible explanations could be that patients randomized to telehealthcare became more aware of their disease and hence used more resources or it could be that especially municipalities discovered patients with an unmet need for e.g. home care when telehealthcare was introduced. Future research planned within this trial would seek to tap into explanations for this difference. It is unknown whether the telehealthcare solution has released its full potential for cost-effectiveness. It is therefore important for healthcare professionals and decision-makers to spend time learning from the experiences gained within the trial in order to investigate if any best practices could be implemented that would increase effectiveness and/or reduce cost without compromising safety and effectiveness.

Future studies

This study indicates that telehealthcare could potentially assist not only in hindering some COPD-related hospital contacts, but also hospital contacts associated with other diseases (incremental costs were reduced by applying all-cause hospital contacts). It could be a coincidence but also due to closer collaboration between healthcare delivery organizations or more frequent monitoring of physical measurements that may also be indicative of other diseases. Future studies should therefore investigate the link between telehealthcare, COPD patients with well-defined comorbidities and hospital contacts.

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Average cost-effectiveness estimates applied in this and other studies could in general hide important sources of heterogeneity. Not much is known on prognostic criteria (e.g. socio-demographic-, geographic-, lifestyle- or health characteristics of the patients) for cost-effectiveness of telehealthcare to chronically ill patients, so further heterogeneity studies should be conducted and are also planned within this trial.

Telehealthcare is a complex intervention involving not only a broad class of technologies, but also organizational infrastructures, actions of healthcare professionals and patients. Experimental evaluation research has been criticized for being a-theoretical in nature in trying to understand why and under what circumstances complex interventions are (un)likely to lead to desired outcomes (60). In this study, mechanisms leading to higher health-related quality of life and cost in the telehealthcare group has largely been treated as a black-box, where patient education, monitoring, emotional support, assisted planning etc. could all have an effect (13). We would recommend, that future cost-effectiveness studies are more informed by a program theory, such as the TECH model (61) that were used in the Healthlines cost-effectiveness studies (62,63). These studies explicitly sought to describe implementation context or account for the causation of the most important telehealthcare-activities that were most likely to activate mechanisms that could lead to “efficient” design and deployment of telehealthcare. However, context and mechanisms that specifically gave rise to between-arm differences in EQ-5D in the Healthlines studies are difficult to identify, reflecting that program theories are often focused on explaining trial-related aspects or outcomes (e.g. smoking cessation or weight loss). In the future, context and mechanisms leading to between-arm differences in EQ-5D and costs should receive more attention in program theory development.

ACKNOWLEDGEMENTS

The authors would like to thank the participants for their time and effort in conduction physical measurements and completing study questionnaires. Also thanks to the North Denmark Region, the 26 municipality districts and around 344 general practitioners in the region for facilitating the implementation the trial.

DECLARATIONS

Detailed description of intervention and comparator: The study protocol includes a detailed description of the intervention and comparator. The study protocol is freely available and can be found at <http://www.trialsjournal.com/content/15/1/178>.

Details of contributors: OH is the principal investigator for the TeleCare North trial and LHE is lead investigator for the economic evaluation in the trial; LHE and OH planned the overall trial design and are guarantors of the statistical quality for the trial as a whole. FWU and PHL contributed to the detailed planning of the data collection of trial questionnaires. FWU planned and collected register data. FWU planned and conducted all analyses under the supervision of LHE and OH. FWU reported the analyses. All authors met regularly during and after the trial period and contributed as a whole to interpreting and the presentation of the data. All authors reviewed and approved the manuscript. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding: This is an independent manuscript commissioned and jointly funded by North Denmark Region, the 26 municipality districts in North Denmark Region, The Obel Family Foundation, the Danish Agency for Digitalization Policy and Strategy, the European Social Fund and Aalborg University.

Competing interests: There are no competing interests. All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author).

Ethical approval: The study is conducted in accordance with the Helsinki Declaration. The trial has been presented to the Regional Ethical Committee for Medical Research in the North Denmark Region where it was determined that no ethical approval was necessary. The trial has also been authorized by the Danish Data Protection Agency. All patients signed an informed consent form before taking part in the clinical trial.

Data sharing: No additional data available

Transparency: OH and LHE affirm that the manuscript is an honest, accurate, and transparent account of the study being reported and no important aspects of the study have been omitted.

FIGURE LEGENDS

Figure 1: Cost-effectiveness acceptability curve in the base-case analysis

Figure 2: Cost-effectiveness acceptability curves for sensitivity analyses

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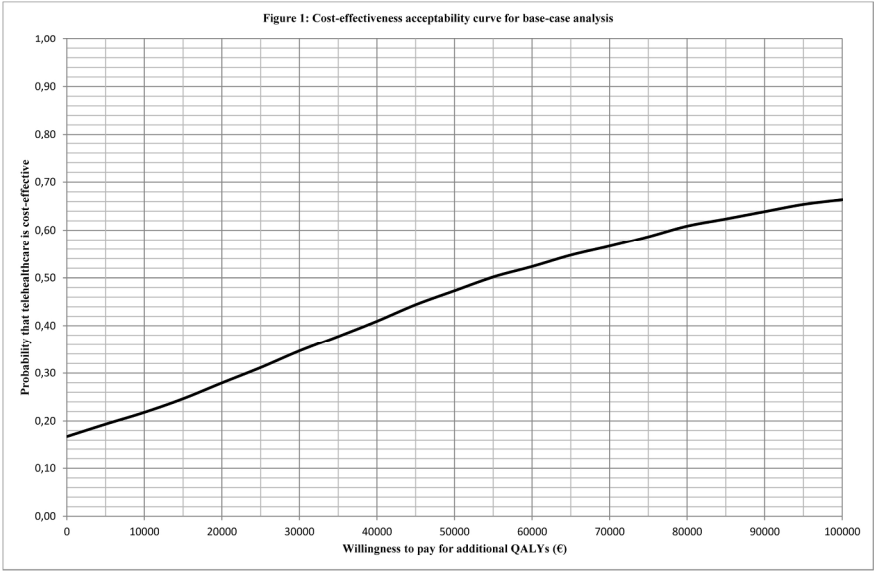
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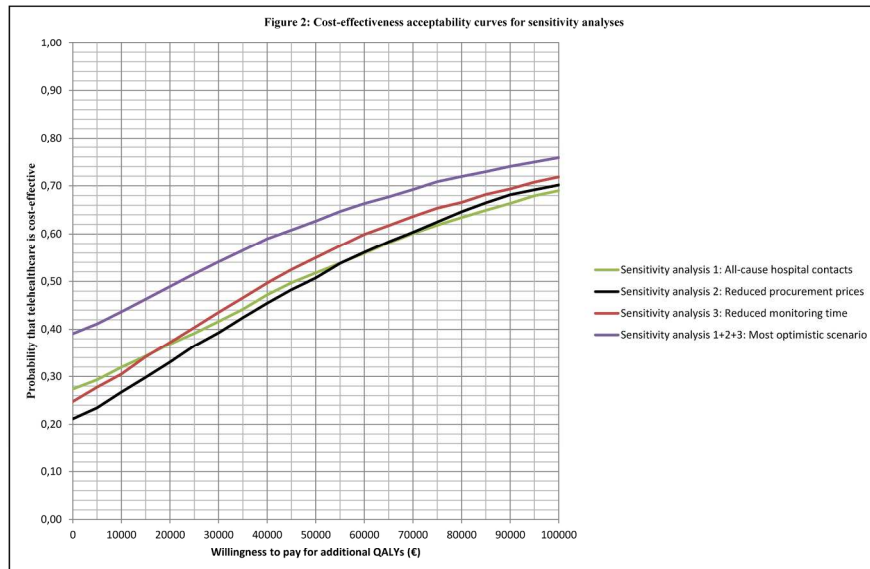
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Additional file 1

Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Checklist
Items to include when reporting economic evaluations of health interventions

Section/Topic	Item No	Recommendation	Reported on page No / Line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared.	P1, 1 sentence
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	P2
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Study protocol P4, L1-18
		Present the study question and its relevance for health policy or practice decisions.	Study protocol P4, L19-22
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Study protocol Table 2
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Study protocol Table 1
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Study protocol P2, L12 P5, L3
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Study protocol Table 1
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Study protocol P2, L3 P5, L2
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	P8, L4
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Study protocol P8, L13-19
Measurement of effectiveness	11a	<i>Single study-based estimates:</i> Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Study protocol
	11b	<i>Synthesis-based estimates:</i> Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	N/A

Measurement and valuation of preference-based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	N/A
Estimating resources and costs	13a	<i>Single study-based economic evaluation:</i> Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	P6, L1 to P8, L6
	13b	<i>Model-based economic evaluation:</i> Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	N/A
Currency, price data, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	P8, L7
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	N/A
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	N/A
Analytic methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	P9, L21 to p10, L7
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 2 Table 3 Table 4
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 5
Characterizing uncertainty	20a	<i>Single study-based economic evaluation:</i> Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	Table 5 Figure 1 Figure 2 P15, L1-L13
	20b	<i>Model-based economic evaluation:</i> Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	N/A
Characterizing heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	N/A
Discussion			
Study findings, limitations, generalizability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	P15, L14 to end P16 to p19
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis.	P20

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		Describe other non-monetary sources of support.	
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	P20

For peer review only